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Antagonists in the Medical Management of Opioid Use Disorders: Historical and Existing Treatment Strategies

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Background and Objectives: Opioid use disorder (OUD) is a chronic condition with potentially severe health and social consequences. Many who develop moderate to severe OUD will repeatedly seek treatment or interact with medical care via emergency department visits or hospitalizations. Thus, there is an urgent need to develop feasible and effective approaches to help persons with OUD achieve and maintain abstinence from opioids. Treatment that includes one of the three FDA-approved medications is an evidence-based strategy to manage OUD. The purpose of this review is to address practices for managing persons with moderate to severe OUD with a focus on opioid withdrawal and naltrexone-based relapse-prevention treatment.
Methods: Literature available on PubMed was used to review the evolution of treatment strategies from the 1960s onward to manage opioid withdrawal and initiate treatment with naltrexone.
Results: Emerging practices for extended-release naltrexone induction include the use of agonist tapers and adjuvant medications. Clinical challenges frequently encountered when initiating this therapy include managing withdrawal and ongoing opioid use during treatment. Clinical factors may inform decisions regarding patient selection and length of naltrexone treatment, such as recent opioid use and patient preferences.
Conclusions and Scientific Significance: Treatment strategies to manage opioid withdrawal have evolved, but many patients with OUD do not receive medication for the prevention of relapse. Clinical strategies for induction onto extended-release naltrexone are now available and can be safely and effectively implemented in specialty and select primary care settings. (© 2018 The Authors. *The American Journal on Addictions* Published by Wiley Periodicals, Inc. on behalf of The American Academy of Addiction Psychiatry (AAAP);27:177–187)

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INTRODUCTION

A drug overdose crisis exists in the United States, with the majority (>60%) of deaths involving an opioid such as heroin, fentanyl, and carfentanil.[1] The 2016 National Survey on Drug Use and Health survey indicated that, within the past year, approximately 2 million Americans aged 18 or older had an opioid use disorder (OUD) involving prescription pain relievers or heroin.[2] OUD is a chronic and relapsing condition with severe health, social, and societal consequences; many who develop it repeatedly seek treatment or interact with medical care via emergency department visits or hospitalizations for infections, overdoses, or other substance-related complications. Moderate to severe OUD as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*)[3] roughly corresponds to opioid dependence as defined by the *DSM-IV*[4] and will be addressed in this review.

Extensive evidence reveals that pharmacotherapy with an opioid receptor agonist (methadone), partial agonist (buprenorphine), or long-acting injection formulation of the opioid antagonist naltrexone (XR-NTX) improves outcomes in patients treated for OUD. The most common treatment approach to OUD involves opioid cessation and management of opioid withdrawal, typically a week-long process also known as "detoxification," followed by relapse-prevention psychosocial therapy in residential or outpatient settings, with encouragement to participate in self-help groups. Psychosocial therapy helps patients adopt healthier nondrug-using lifestyles, with medications providing further symptomatic support during this lengthy transition.

Although an approach that does not include medications to prevent relapse works for some patients (e.g., those treated in long-term residential programs),[5] evidence has repeatedly associated this approach with high rates of relapse and complications, including fatal overdose.[6] Thus, clinical experts favor OUD treatments that include maintenance medications because they are consistent with evidence and constitute adequate care.[7,8]

Pharmacological management usually involves maintenance treatment with an opioid receptor agonist or a partial agonist, and this approach has the most extensive evidence supporting its long-term effectiveness.[7] An advantage of agonist treatment is that it can be started in outpatients while minimizing the severity and duration of opioid withdrawal. Both methadone and buprenorphine are listed by the World Health Organization (WHO) as essential medications to treat OUD; in the United States, both are approved by the US Food and Drug Administration (FDA) for the treatment of opioid dependence/addiction. Methadone and buprenorphine have been shown to increase adherence to antiretroviral therapy in HIV-infected drug users[9] and to increase treatment retention of opioid-dependent pregnant women.[10] Recently, longer-acting formulations of buprenorphine have been developed, including a monthly injection. Additional research is ongoing to evaluate an extended-release buprenorphine implant in Phase 3 randomized clinical trials.[11]

An alternative strategy involves treatment with an opioid receptor antagonist such as naltrexone. Naltrexone administration requires prior completion of opioid withdrawal, typically with 7–10 days having passed since the last opioid dose; otherwise, it may precipitate significant opioid withdrawal. Oral naltrexone, a formulation that requires daily administration, has been available for clinical use in the United States since the 1970s. It is recognized in WHO treatment guidelines for preventing relapse in patients who have withdrawn from opioids[8] and is FDA-approved for the blockade of the effects of exogenously administered opioids. However, problems with adherence to a daily medication regimen followed by treatment dropout have limited the effectiveness of oral naltrexone in clinical practice. In 2010, an extended-release injectable naltrexone (XR-NTX) formulation that provides an opioid blockade for approximately 1 month after a single dose was FDA-approved for the prevention of relapse to opioid dependence following opioid detoxification as part of an individualized comprehensive management program that includes psychosocial support.[12]

This long-acting formulation can be given in a wide range of clinical settings, including primary care and criminal justice systems.[13,14] However, there is limited experience with this drug medication outside specialized treatment settings. XR-NTX has frequently been offered to patients who have completed extended residential treatment[15] and to patients for whom initiation of relapse-prevention treatment with XR-NTX was relatively uncomplicated because of current abstinence.[16] Most patients in need of treatment, however, are actively using opioids at the time of initial evaluation and require completion of opioid withdrawal before XR-NTX initiation. Although medically supervised management of withdrawal in the inpatient setting is optimal, the availability of inpatient treatment in the United States is limited and where it exists is often restricted to a few days. Therefore, feasible and effective outpatient approaches to manage opioid withdrawal for patients seeking treatment with XR-NTX are needed.

This review describes the evolution of treatment strategies to manage opioid withdrawal and initiate treatment with XR-NTX, with a focus on the outpatient setting, and discusses emerging XR-NTX induction practices, challenges frequently encountered when initiating XR-NTX, and clinical factors helpful in identifying patients suitable for opioid antagonist treatment. Literature available on PubMed was used to review the evolution of treatment strategies from the 1960s onward to manage opioid withdrawal and initiate treatment with naltrexone.

HISTORICAL PERSPECTIVE ON CLINICAL MANAGEMENT OF OPIOID WITHDRAWAL AND INITIATING TREATMENT WITH NALTREXONE

Medical management of OUD has continued to evolve since the first widespread treatments were introduced in the 1960s (Fig. 1). For many years, medical management of OUD

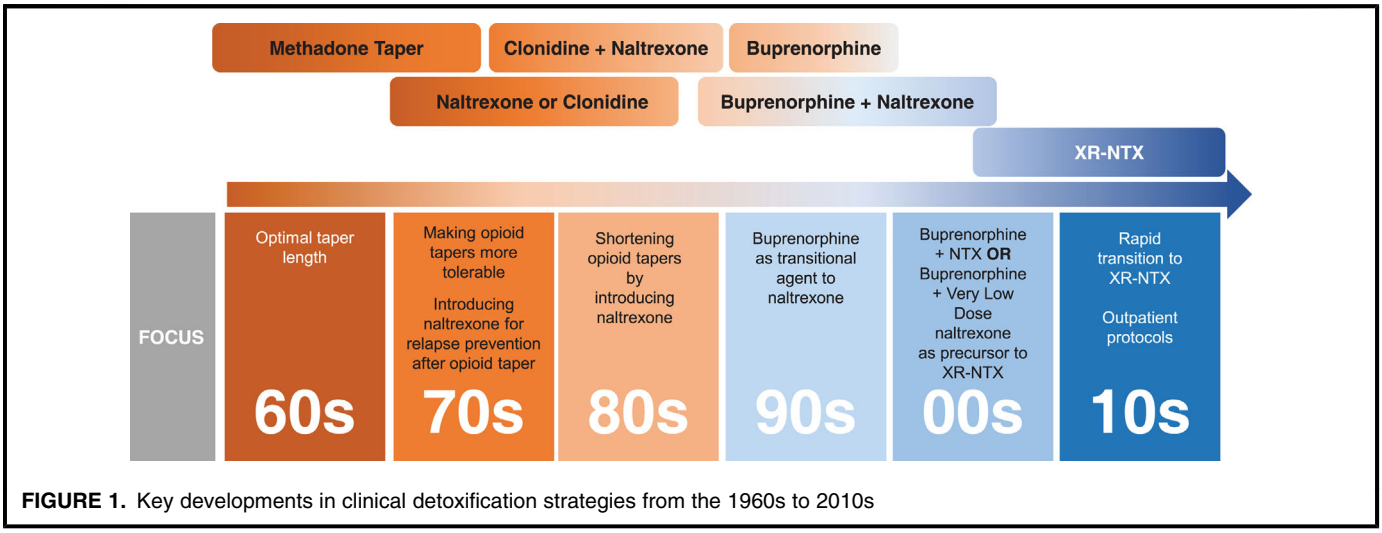

FIGURE 1. Key developments in clinical detoxification strategies from the 1960s to 2010s

has focused on alleviating withdrawal[17]; however, this approach has been repeatedly shown to be insufficient for ensuring long-term abstinence. OUD is now recognized as a chronic disorder that persists beyond the acute withdrawal period and, therefore, is insufficiently managed with short-term interventions. Observable neuroadaptive changes in the brain may explain the high levels of relapse that characterize substance use disorders.[18] Medications have been developed to address these changes and treat OUD. In addition, patient education and counseling to reduce the ongoing impact of OUD are important for increased adherence and improved treatment outcomes.

However, medication-based approaches for the long-term management of OUD are underutilized because, despite clear evidence that short-term medication treatments are insufficient, practitioners and treatment programs often focus on alleviating acute withdrawal and discontinuing medication support once acute opioid withdrawal has resolved. Accordingly, rates of opioid use resumption and overdose among patients treated for OUD remain high.[19]

Gradual Methadone Taper: 1960s and 1970s

A major advance in OUD treatment was the introduction of methadone maintenance in the early 1960s as a strategy to reduce drug use, mortality, morbidity, and other adverse consequences of heroin addiction. Methadone was initially proposed as a time-limited approach; when patients achieved treatment goals and wanted to discontinue medication support, standard practice involved a slow dose taper over 14–180 days.[20–22] Using this approach, anywhere from 8% to 79% of patients achieved an opioid free state, with the proportion of patients remaining opioid free generally decreasing with longer periods of observation.[23] Further research indicated that a longer tapering period increased treatment retention, but even with longer tapers, intolerable withdrawal and craving were not eliminated and led some patients to discontinue treatment, resume illicit opioid use, or ask that the dose tapering be stopped or reversed.[22,24] In summary, time-limited use of methadone puts patients at risk and should generally be avoided, regardless of the schedule of methadone discontinuation.

Clonidine: Late 1970s to Early 1980s

Low rates of methadone discontinuation and persisting discomfort despite very slow tapers led to the use of adjunctive "non-opioid" medications that targeted residual signs and symptoms of opioid withdrawal. Beginning in the 1970s, these efforts aimed to reduce hyper-arousal and anxiety, both dominant features of opioid withdrawal, by decreasing adrenergic transmission. Clonidine, an α-2 adrenergic agonist, was found to achieve these results via inhibiting noradrenergic activity in the locus coeruleus, and enabled some patients to discontinue chronic methadone treatment during a 14-day inpatient treatment episode.[25] However, concerns arose that higher doses of clonidine were often needed to suppress withdrawal, producing significant hypotension while offering only partial relief of the discomfort, craving, and other symptoms of withdrawal, resulting in treatment dropout and relapse.[26] However, clonidine continues to be used as an adjunct during opioid withdrawal to provide limited symptomatic relief.

Naltrexone: 1970s

As clinical observations and studies repeatedly found that completing opioid withdrawal was insufficient to assure continuing abstinence, in the 1970s a new approach was proposed that involved naltrexone, an opioid receptor "blocker," to prevent relapse after detoxification.[27] Clinical trials evaluated oral naltrexone as a relapse-prevention strategy.[28] Initiation of naltrexone treatment, defined as tolerating 50 mg, was identified as a useful "endpoint" for opioid-withdrawal treatment.[29] The main challenge was that introducing naltrexone too early following opioid discontinuation precipitated withdrawal. An additional challenge was poor adherence to daily dosing and resultant treatment dropout during the first weeks of treatment, as patients continued to experience cravings and symptoms of protracted withdrawal, which they often attributed to naltrexone.[30]

Clonidine + Naltrexone: 1980s

Clonidine and other adjunctive medications rendered the patient experiencing withdrawal more comfortable, but did not shorten its duration.[26] Although administering a low dose of an opioid receptor antagonist (naloxone or naltrexone) shortened withdrawal by 2–4 days, withdrawal symptom severity was exacerbated. Thus began the process of introducing rapid (accelerated) withdrawal by administering naltrexone 1–2 days after the last opioid dose,[31] in combination with adjunctive medications such as clonidine and benzodiazepines, to ameliorate the symptoms of withdrawal.[29,32]

The naltrexone plus clonidine regimen was refined throughout the 1980s and first used in an inpatient setting with methadone-maintained patients. As the usual daily dose of naltrexone (50 mg/day) was too high for use within 1 or 2 days of opioid cessation, in these early studies, clonidine was administered from the first day of treatment, and naltrexone (at starting doses of 1–12.5 mg/day) was introduced on the second day and rapidly up-titrated to 50 mg by Day 5.[29,33–35] Doses of adjunctive clonidine and benzodiazepines continued to be administered, as needed, for anxiety, or insomnia at decreasing doses.[29] This protocol was later amended to include standing doses of benzodiazepines and other medications to decrease muscle pain and gastrointestinal hypermotility.[36] Subsequent studies further supported the use of non-opioid medications in managing withdrawal from methadone and heroin, in both inpatient and outpatient settings.[34,37]

Clonidine + Naltrexone + Buprenorphine: Late 1980s–1990s

Buprenorphine, a partial opioid receptor agonist with a long half-life, was first proposed as an OUD treatment in the late

1970s.[38] Although several studies showed that gradual outpatient buprenorphine tapers result in low rates of opioid abstinence (7–22% at 1 month),[39–41] buprenorphine as maintenance therapy or for use in transition to other medications resulted in greater success. Patients treated with buprenorphine for the discontinuation of methadone or heroin exhibited milder withdrawal symptoms; therefore, buprenorphine gained acceptance as a medication that enabled easier transition onto naltrexone.[23,42–45]

Combining Opioid Agonists With Very-Low-Dose Naltrexone: 1990s–2000s

The use of very-low-dose (<1 mg) naltrexone to assist with opioid withdrawal evolved from the observation of a methadone-maintained patient who accidentally ingested 50 mg of naltrexone and after an initial period of withdrawal remained symptom-free, even with significant blood levels of both drugs.[46] The observation spurred the development of a very-low-dose naltrexone paradigm wherein patients received increasing doses of naltrexone, starting at .125 mg and reaching a full therapeutic dose of 50 mg, while concurrent methadone was rapidly tapered. Adjuvant medications were also used and the procedure was accomplished within 6 days.[46–48] However, while very-low-dose naltrexone reduced withdrawal and craving, treatment retention or success was not improved.[49,50]

Naltrexone + Buprenorphine as Precursors to Extended-Release Naltrexone: Early 2000s

The early and mid-2000s saw a revival of naltrexone induction studies, primarily due to potentially improved treatment adherence with extended-release formulations of naltrexone. Newer protocols focused on identifying optimal doses and treatment durations of buprenorphine, naltrexone, and clonidine to shorten induction periods, while minimizing the severity of withdrawal. Major changes to earlier protocols involved reducing buprenorphine treatment to 1–2 days, shortening to 1 day the "washout" period before starting naltrexone, and decreasing the first dose of naltrexone from 12.5 to 3 mg, with supportive medications, usually standing doses of clonidine and clonazepam administered at frequent dosing intervals.[51–57] A 2017 study comparing outpatient detoxification regimens showed that an oral naltrexone-assisted detoxification regimen, compared with a descending buprenorphine taper followed by a 7-day washout period, was more likely to lead to successful XR-NTX induction (56% vs. 33%) and a second XR-NTX dose (50% vs. 27%).[58]

Extended-Release Naltrexone: 2010s

Many patients starting treatment with oral naltrexone have difficulty adhering to a daily regimen,[59,60] a pattern often correlated with poor treatment retention and relapse.[61,62] Poor adherence to daily oral medication spurred the development of extended-release injectable and implantable formulations that would eliminate the need for daily decisions to take a medication.[53,63–67]

XR-NTX is a 380-mg dose of naltrexone-containing biodegradable microspheres administered as suspension by monthly intramuscular injections approved by the FDA in 2010 as Vivitrol for prevention of relapse to opioid dependence. Naltrexone implants have been developed and used in Australia,[68] and one[69] is approved and used in Russia. In the United States, compounding pharmacies have manufactured implants, but none has received FDA approval.

Patients treated with XR-NTX (implants or injectable) have less treatment dropout, lower rates of opioid use, and reduced craving, as compared with patients treated with placebo.[53,64,70] Persons on probation or parole who were randomly assigned to an open-label treatment with XR-NTX compared with treatment as usual had significantly lower rates of relapse, longer relapse-free survival, lower rates of heroin use, and fewer overdoses over a 24-week treatment period, with a loss of effect seen at 28 and 54 weeks after the end of treatment.[71] A study using historical controls found that patients treated with XR-NTX had higher retention rates and less relapse than patients treated with oral naltrexone.[72] Recent studies directly comparing the efficacy of XR-NTX and buprenorphine/naloxone show that among patients who successfully initiated treatment with medications, treatment outcomes were comparable.[73,74]

CURRENT APPROACH TO TREATMENT OF OPIOID USE DISORDER: CHOOSING THE PHARMACOLOGICAL APPROACH

Although long-term follow-up data may be available for individual medications,[75,76] limited data are available from controlled studies or long-term observational cohort follow-up studies providing head-to-head comparisons of medications for managing OUD. Treatment availability, health coverage limitations, or a patient's preferences often determine the treatment used. Nevertheless, it is important that the provider engage the patient in a process of shared decision-making to arrive at the most appropriate treatment plan, involving a discussion of all available treatments including residential, office-based pharmacotherapy, and addiction treatment programs that offer FDA-approved medications. Important discussion topics include the differences among methadone, buprenorphine, and naltrexone; requirements for treatment initiation; risks; benefits; side effects; possible interactions with other medications; the chronic nature of treatment; treatment dropout or termination issues; and the logistics associated with various treatment options (e.g., daily visits for methadone; less often for buprenorphine; monthly visits for XR-NTX). When possible, the final discussion should involve a family member or significant other to facilitate adherence. The provider may assess the patient's motivation for treatment and medication preferences before offering a final recommendation for a specific medication, along with alternatives if there are problems with the first choice.[7] In cases where a provider

lacks expertise or certification, patients can be referred to another provider.

Methadone maintenance is the most studied approach and should be offered to all patients seeking treatment for OUD. Patients who have previously found methadone effective should be encouraged to continue using methadone maintenance.[8] Although many patients will opt for agonist treatment,[77] some do not want it, will only seek treatment in settings where it is unavailable, agree only to short-term agonist treatment, or will want to try something else.[78] For these patients, evidence largely suggests that a slow agonist taper provides superior outcomes to a rapid taper, although conflicting results have been reported.[39,79] Some patients, however, despite having been successfully treated with agonists long-term, may be unable to complete the taper and may have to resume agonist maintenance. Others will only agree to short-term agonist treatment to alleviate withdrawal, despite having experienced its high failure rate. For these patients, XR-NTX may represent a viable treatment.

Initiating Antagonist Treatment With Extended-Release Naltrexone (Induction)

Despite its demonstrated efficacy, tolerability, and monthly dosing, XR-NTX remains underutilized in community-based treatment programs.[80] Reasons include the novelty of this approach, a small number of published effectiveness trials, high dropout rates from oral naltrexone in earlier studies, low penetration into formularies, and concerns about treatment cost. Other reasons include lack of knowledge and experience of providers, particularly regarding strategies to initiate treatment safely, alleviate distress associated with early abstinence, and provide concurrent psychosocial treatment to address lifestyle changes and use of alcohol and non-opioid drugs. Strategies to increase the success of transition of active opioid users onto XR-NTX treatment remain key to the success of long-term relapse-prevention treatment.

Initiating XR-NTX treatment is relatively straightforward in patients who are not physiologically dependent on opioids, such as persons leaving a controlled setting (e.g., residential treatment program or correctional facility). The first dose of XR-NTX can be administered once the patient is confirmed to be abstinent from opioids by urine toxicology, and the clinician may give an optional naloxone challenge to confirm the resolution of physiological dependence. Because of buprenorphine's tighter binding to opioid receptors, naloxone may not precipitate withdrawal in patients using buprenorphine, highlighting the need to ensure that urine drug testing includes testing for buprenorphine. In our experience, a trial period of treatment with oral naltrexone is not recommended prior to the first XR-NTX injection because patients are less likely to adhere to it and experience relapse. Some practitioners, however, may choose to administer a single dose of 25–50 mg oral naltrexone after establishing the absence of physiological opioid dependence, to confirm tolerability, and then provide the first XR-NTX injection 1–2 hours later.[81] It should be noted that a recent study demonstrated that, when used for 1–7 days as a detoxification agent, buprenorphine may not require a subsequent 7-day washout period.[58]

However, most patients presenting for treatment are actively using opioids at the time of evaluation. In such patients, initiating XR-NTX treatment requires that the patient first complete opioid withdrawal. To minimize the risk of precipitated withdrawal, it is recommended that patients have at least 7–10 days of washout after their last use of opioids. The patient then receives an injection of 380 mg XR-NTX provided the absence of physiological dependence is confirmed by urine testing and naloxone challenge. A common procedure involves a short-term (eg, 7- to 14-day) buprenorphine taper followed by 7–10 days of washout prior to the first XR-NTX dose (Table 1). To reduce the risk of premature treatment dropout and relapse, a shorter induction is preferable if the risk of precipitated withdrawal can be avoided or minimized.[59]

Two procedures may shorten the induction period following abrupt opioid agonist discontinuation. First, buprenorphine can be given for 1 day, as it replaces the full agonist at the receptor, while providing partial agonist activity to prevent significant withdrawal. Buprenorphine is then followed by 1–2 days of washout and a gradual ascending titration of oral naltrexone over the subsequent 3–5 days, beginning with a low dose of 1–3 mg.[82] Throughout this procedure, patients receive standing doses of adjunctive medications, usually clonidine and clonazepam (Table 1).[58,82] The second procedure employs buprenorphine taper in combination with very low doses of oral naltrexone ($\leq$1 mg/day) over the first 2–3 days, followed by a gradual up-titration of naltrexone to full blocking doses ($\geq$25 mg/day), usually accomplished within 7 days[83] (Table 2). These procedures have allowed 50–70% of outpatients to successfully initiate treatment with XR-NTX[58,83] with favorable tolerability and no serious adverse events due to precipitated withdrawal.[52,55,56,83]

Stabilizing Patients on Extended-Release Naltrexone

XR-NTX should be part of an individualized comprehensive management program that includes psychosocial support.[52,84] Initiation of treatment with XR-NTX shortly after completion of opioid withdrawal, or lack of confirmation of the absence of current opioid dependence or recent buprenorphine use, may result in protracted withdrawal-like symptoms for several weeks.[30] Symptoms can include sleep disturbances, low energy, anxiety, irritability, and diarrhea that slowly resolve over days to weeks.[52,57] To alleviate protracted withdrawal, several medication strategies have been proposed, including methylphenidate[85] and quetiapine,[86] and cannabis may also have a therapeutic benefit.[57]

Managing Ongoing Opioid Use in Patients Being Treated With Extended-Release Naltrexone

Up to one third of patients who receive XR-NTX use illicit opioids at some point during treatment, commonly as single

TABLE 1. Initiating treatment with extended-release naltrexone (inpatient and outpatient)

Day	Standard induction procedure	Inpatient procedure with 1 day of BUP[52,56]	Outpatient procedure with 1 day of BUP[58]
1	Patients instructed to remain abstinent for 7–10 days from all opioids except those prescribed as part of the induction protocol	Induct and administer buprenorphine 8 mg	Patient comes to clinic in mild–moderate withdrawal. Give buprenorphine starting at 2 mg, titrate up to 8 mg as tolerated
2		Washout days	Washout day
3			Initiate titration of oral naltrexone* (total daily doses):
4		Increase daily doses of oral naltrexone*: 3.125, 6.25, and 25 mg	1, 3, 12, and 25 mg
5			
6			
7		Administer XR-NTX 380 mg injection	Administer XR-NTX 380 mg injection
Day 8–11	Administer naloxone challenge followed by XR-NTX 380 mg injection		
As needed	Adjuvant medications: clonidine, clonazepam, prochlorperazine, trazodone, zolpidem		

BUP, buprenorphine; XR-NTX, extended-release naltrexone.
*Doses of naltrexone less than 50 mg are not commercially available and require a compounding pharmacy for dispensing.

episodes to "test" the blocking effect of the medication.[53–86,62] A recent study of patients using opioids during XR-NTX blockade found that most did not feel euphoria and used lower doses than before receiving XR-NTX. Most patients reported testing the blockade during the first weeks after the injection (median, 2.4 weeks).[87] Some patients continue using opioids for several weeks after XR-NTX induction, but this practice usually has not been associated with worse long-term outcomes and rarely continues if the patient receives XR-NTX as scheduled.[88] Based on our clinical experiences, continuous blockade prevents patients from becoming physiologically re-dependent, and many patients prefer to remain on XR-NTX despite occasional brief episodes of use. Very few patients appear to intentionally "override the blockade." However, an attempt to override the blockade may lead to opioid intoxication or fatal opioid overdose, a fact that should be communicated to patients. Last, patients with OUD treated with XR-NTX or naltrexone implant report reduced craving,[53,64,70] an effect possibly related to blocking beta-endorphin release in response to triggers or cues.[89]

Safety of Long-Term Treatment With Extended-Release Naltrexone

XR-NTX is generally well tolerated in patients with OUD. Adverse events may include injection site pain, nausea, headaches, nasopharyngitis, insomnia, and toothache.[12] A recently completed 2-year open-label study of healthcare professionals with opioid dependence showed XR-NTX to have levels of safety similar to those seen in shorter-term studies.[90]

Vulnerability to an overdose is an important consideration in patients with OUD who drop out of antagonist or agonist treatment. In the case of naltrexone, after opioid detoxification or if a scheduled dose is missed, patients have reduced tolerance to opioids and are vulnerable to overdose. Although opioid antagonists up-regulated μ-receptors and induced supersensitivity to morphine in a mouse model,[91] healthy humans show no evidence of μ-receptor up-regulation in the respiratory control system, the most likely site of opioid overdose lethality.[92] Overall, the risk of overdose is significantly lower in patients who are actively involved in medication-assisted treatment whether it is with methadone, buprenorphine, or naltrexone.[93] Attempts to override the antagonist blockade, however, can result in fatal overdose,[11] which should be discussed with patients at each treatment visit.

In a recent 6-month randomized study with a 78-week follow-up period, no overdoses were reported in the 153 enrolled patients treated with XR-NTX, compared with seven overdoses in the treatment-as-usual group (brief counseling and referrals for community treatment programs).[71] Patients treated with oral naltrexone had a higher risk of overdose than those treated with methadone[94] or naltrexone implants[95]; the risk was comparable in patients maintained on methadone or naltrexone implants.[96] In two recent large comparative effectiveness trials of XR-NTX versus buprenorphine-naloxone, risk of overdose was similar

TABLE 2. Using very low doses of naltrexone to initiate treatment

Day	Outpatient procedure[83]
	Patients instructed to remain abstinent for 24 hours from all opioids except those prescribed as part of the induction protocol
1–3	Increase daily dose of oral naltrexone (.25–1 mg)* as tolerated, decrease daily dose of buprenorphine (4–2 mg)
4–7	Discontinue buprenorphine and increase daily dose of naltrexone to 30–50 mg by Day 7
8	Administer XR-NTX 380 mg injection
As necessary	Adjuvant medications: trazodone, cyclobenzaprine, lorazepam, hydroxyzine

XR-NTX, extended-release naltrexone.

*Doses of naltrexone less than 50 mg are not commercially available and require a compounding pharmacy for dispensing.

in the XR-NTX ($n = 2/283$ and $n = 0/71$, respectively) and buprenorphine ($n = 3/287$ and $n = 1/72$, respectively) groups.[73,74] Notably, patients dropping out of treatment with methadone or buprenorphine were also at elevated risk of overdose.[97,98]

Clinicians are advised to monitor patients on XR-NTX for the emergence of depressive symptoms. In a 24-week trial of XR-NTX for alcohol dependence ($N = 624$), depressive symptoms were reported by 10% of patients treated with XR-NTX, compared with 5% of patients treated with placebo.[99] However, depressed mood or suicidal thinking was not reported by patients treated with either XR-NTX or placebo in the pivotal XR-NTX trial ($N = 250$),[64] and psychiatric adverse effects occurred at comparable rates in recent reports of patients treated with buprenorphine and XR-NTX.[73,74] Studies have demonstrated that depressive symptoms, often present at treatment entry, improve with opioid abstinence whether in the setting of receipt of oral naltrexone, XR-NTX, or placebo.[70,100,101] Adherence to oral naltrexone has been associated with fewer depressive symptoms than non-adherence[102] and depressive symptoms improved significantly during the first month of treatment with XR-NTX.[103]

Selection of Patients Suitable for Extended-Release Naltrexone

Patients who have been successfully treated with opioid agonists but would like to taper off them may be suitable candidates for XR-NTX because discontinuation of opioid agonist treatment frequently leads to relapse.[77,104] According to a recent survey of patients undergoing opioid withdrawal, patients preferred XR-NTX (32%) over buprenorphine (28%) or methadone (18%),[77] underscoring the importance of presenting patients seeking treatment for OUD with the full range of agonist and antagonist choices.

A secondary analysis of the pivotal study that led to FDA approval of XR-NTX for opioid dependence[65] did not reveal any baseline patient characteristics associated with treatment outcome,[105] although particularly severe, unstable psychosocial conditions may interfere with retention.[106] Because most trials have been conducted in adults, limited information is available on adolescents and young adults.[107,108] Chronic pain[109] poses an additional challenge in using antagonists. More research is needed to understand the risks associated with naltrexone during pregnancy[110] although recent data suggest comparable obstetric outcomes.[111] XR-NTX may be used in patients with mild renal or mild/moderate hepatic impairment with no dose adjustments.[12]

Oral naltrexone and XR-NTX have been shown to benefit patients who are motivated for abstinence due to employment-based negative contingencies, such as healthcare professionals or business executives.[90,112,113] Combining XR-NTX with employment-based reinforcement has also been shown to be effective in unemployed adults.[114] Others who may benefit include incarcerated persons and those without access to opioid agonist treatment.[60,71,115] Criminal justice offenders treated with XR-NTX had double the median length of opioid-free time compared with those who received brief counseling and a referral to community treatment.[71] Positive outcomes extended to offenders with multiple diagnoses, including HIV[116] and drug court-involved persons.[117]

SUMMARY AND FUTURE DIRECTIONS

(1) This review aimed to describe the evolution of treatment strategies to manage opioid withdrawal and to place the use of XR-NTX as a relapse-prevention strategy in OUD into the historical context of several decades of clinical research.
(2) Standard practice for managing OUD remains maintenance treatment with methadone or buprenorphine.
(3) Many patients are treated with medications to alleviate opioid withdrawal but are not offered medication support afterward, a strategy with a high failure rate and a significant risk of overdose.
(4) Clinical strategies for XR-NTX initiation have evolved considerably. Common treatment protocols that address the recommendation for a 7- to 10-day opioid-free duration prior to transitioning to XR-NTX are now available and can be safely and effectively implemented in specialty and select primary care settings.

(5) XR-NTX is generally well tolerated in patients with OUD. Vulnerability to an overdose is an important consideration in patients who drop out of antagonist or agonist treatment or who are detoxified or released from correctional facilities without follow-up medication-assisted treatment.
(6) Suitable candidates for XR-NTX treatment may include patients with OUD who do not want to initiate or continue treatment with an opioid agonist and patients who live where agonists are not easily accessible.

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Declaration of Interest

Adam Bisaga, MD, has received honoraria, consultation fees, travel reimbursement for training, medical editing, market research from UN Office on Drugs, Crime, Motive Medical Intelligence, Healthcare Research Consulting Group, GLG Research Group, Guidepoint Global. Dr. Bisaga received compensation from Indivior for an unbranded educational activity. He received pharmaceutical products extended-release naltrexone from Alkermes for NIH-funded research studies, was an investigator for a multisite clinical trial funded by Alkermes, he served as an unpaid consultant to Alkermes. Paolo Mannelli, MD, received consultation fees from Guidepoint Global and Alkermes, Inc., research funding from Alkermes, and is an investigator for a multisite clinical trial funded by Alkermes. Maria A. Sullivan, MD, PhD, is an employee of Alkermes, Inc. and had received pharmaceutical products (extended-release naltrexone) from Alkermes for NIH-funded research studies. Suzanne K. Vosburg, PhD, is a research consultant and writer who contracts with multiple companies requiring independence of perspective. She contracted with Alkermes, Inc. for preparation of this paper. Peggy Compton PhD, RN, does not have any conflicts of interest. George Woody, MD, has received from Alkermes extended-release injectable naltrexone (VIVITROL) or corresponding placebo control for clinical studies in the United States, Iceland, and Russia, and received honoraria from Alkermes, Inc., and Fidelity Capital has provided implant naltrexone at reduced cost for studies in Russia. Thomas Kosten, MD, has received honoraria from Alkermes, Inc. and is an investigator for a multisite clinical trial funded by Alkermes, Inc.

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