

Injectable extended-release naltrexone for the prevention of relapse to opioid dependence following opioid detoxification

Evgeny Krupitsky*

Practice points

- Injectable extended-release naltrexone (XR-NTX), approved in the USA for the prevention of relapse among detoxified opioid-dependent individuals, was formulated to address the adherence problem that limited the clinical usefulness of oral naltrexone.
- XR-NTX is administered monthly by intramuscular injection by a healthcare professional and should be accompanied by psychosocial counseling.
- A Phase III multicenter, placebo-controlled, randomized clinical trial found XR-NTX to be superior to placebo on all primary and secondary end points.
- Naturalistic analysis of a large healthcare claims database found that total healthcare costs following treatment with XR-NTX were not significantly different from oral naltrexone or buprenorphine, and were 49% lower than with methadone.
- In the Phase III trial, adverse events were mild-to-moderate in severity, with nasopharyngitis, insomnia and injection-site pain occurring more frequently with XR-NTX than placebo. Discontinuations due to adverse events were similar in both groups.
- Unanswered questions include the efficacy of XR-NTX therapy in different settings, such as primary care offices, and the appropriate duration and long-term safety of XR-NTX treatment.

SUMMARY Opioid dependence is a growing, worldwide public health concern. In contrast to opioid μ -agonist (or 'substitution') maintenance treatments, injectable extended-release naltrexone (XR-NTX), approved in the USA and Russia, is an opioid antagonist, formulated to address nonadherence, which limits the utility of oral naltrexone for opioid dependence. This article reviews the clinical trial data underlying the approval of XR-NTX for opioid dependence and the agent's clinical use. XR-NTX met all primary and secondary end points in a multicenter, placebo-controlled trial ($n = 250$) conducted in Russia, with two discontinuations in each group because of adverse events. Cost-effectiveness analysis of

*Department of Addictions, Bekhterev Research Psychoneurological Institute & St Petersburg State Pavlov Medical University, 3 Bekhtereva Street, St Petersburg 192019, Russia; Tel./Fax: +7 812 365 2217; krueator@gmail.com

claims data found that 6-month total healthcare costs following XR-NTX (US\$8582 per patient) were not significantly different from oral naltrexone (US\$8903; $p = 0.867$) or buprenorphine (US\$10,049; $p = 0.414$), and were 49% lower than with methadone (US\$16,752; $p < 0.0001$). Future research should address induction and duration of treatment with XR-NTX.

Opioid dependence continues to be a worldwide problem [101,102]. Prevalence rates for heroin and other opiates range between 0.3 and 0.5% of the world's population aged between 15 and 64 years [101]. A dramatic rise in the non-medical use of opioid pain medications has also been occurring, particularly in the USA, with an estimated 1.9 million Americans abusing or dependent on prescription pain medications in 2010 [1]. Dependence on opioids is associated with increased morbidity and mortality, poor social functioning, economic dependence and crime [2–4]. The economic burden to society of opioid-use disorders is large, with total US societal costs of prescription opioid abuse estimated at US\$55.7 billion in 2007 [5] and total US costs of heroin addiction estimated at US\$21.9 billion in 1996 [6].

Available treatment modalities vary across different countries, with the most common approaches consisting of either agonist maintenance pharmacotherapy or drug-free psychosocial treatment. Maintenance pharmacotherapy options include methadone (a μ -opioid receptor agonist) or buprenorphine (a partial agonist). The efficacy and safety of buprenorphine and methadone are documented by numerous studies [7,8]. In the majority of UN member countries (122 of 192), however, agonist therapy is unavailable or restricted owing to concerns about physiological dependence or abuse and illegal diversion [2]. In addition, agonist therapy is sometimes not the preferred treatment for specific types of patients. This includes young people, those with a brief history of addiction or who are new to treatment, and those whose employment may prohibit opioid use (e.g., healthcare providers, pilots and police, fire, emergency and military personnel). Drug-free psychosocial treatment is an option for these and other patients, but is associated with high rates of relapse [9].

Opioid dependence can also be treated with naltrexone, a μ -opioid receptor antagonist. However, in general, problems with adherence to oral naltrexone have undermined its efficacy in the treatment of opioid dependence [10]. This problem with adherence was anticipated by the US National Institute on Drug Abuse as early as

1976 and led to requests for the development of a long-acting opioid antagonist. Following this request, Alkermes, Inc. (MA, USA) developed a once-monthly extended-release formulation of injectable naltrexone (XR-NTX, Vivitrol®) [11]. XR-NTX gradually releases naltrexone from microspheres composed of medical-grade polylactide-*co*-glycolide, a polymer used in dissolvable surgical sutures. This article will review the clinical trial data on which approval of XR-NTX for opioid dependence was based, and present information on its administration, clinical pharmacology, mechanism of action, pharmacodynamics, pharmacokinetics and its associated adverse events and labeled warnings.

Indications & usage

In its oral form, naltrexone was approved by the US FDA for treatment of opioid dependence in 1984. The extended-release formulation was approved more recently (October 2010) in the USA for prevention of relapse to opioid dependence among detoxified individuals as part of a comprehensive management program that includes psychosocial support. Prior to its approval for opioid dependence, XR-NTX was approved for use in the treatment of alcohol dependence in both the USA and Russia.

XR-NTX is contraindicated in patients with acute hepatitis or liver failure, patients receiving opioid analgesics, patients with current physiologic opioid dependence, patients in acute opioid withdrawal, any individual who has failed a naloxone challenge test or has a positive urine screen for opioids, and patients who have previously exhibited hypersensitivity to naltrexone, polylactide-*co*-glycolide, carboxymethyl cellulose or any other components of the diluent.

Dosage & administration

The standard dosage of XR-NTX is 380 mg delivered as an intramuscular gluteal injection. Injections are delivered every 4 weeks (or once a month) by a healthcare professional. It is recommended that injections be administered in alternating buttocks over the course of treatment. If a dose is missed, the next dose should be administered as soon as possible. To assure proper release kinetics and avoid microsphere particle entry

into the circulatory system, XR-NTX should never be administered intravenously.

It is not required that patients be pretreated with oral naltrexone before beginning XR-NTX injections, however, patients should be opioid free for 7–10 days prior to treatment with XR-NTX.

Clinical pharmacology

■ Mechanism of action

Naltrexone, and its active metabolite 6- β -naltrexol, are antagonists with a high affinity for the μ -opioid receptor. The clinical efficacy of naltrexone results from blocking the effects of opioids through competitive binding at these receptors. The ability of XR-NTX to sustain a blockade of opioid receptors in opioid abusers over the month following an injection was recently demonstrated in an opioid challenge experiment [12]. In this study, low subjective ratings of ‘any drug effect’, indicating blockade, were maintained for a full 28-day period for each of three dosage levels that were tested in the experiment (75, 150 and 300 mg) of XR-NTX, and the FDA-approved formulation is marketed at a higher naltrexone dose (380 mg).

With XR-NTX, extended release is achieved through the embedding of naltrexone within a matrix of microspheres (<100 μ m diameter) made of polylactide-*co*-glycolide. Polylactide-*co*-glycolide is a common biodegradable copolymer that has been used safely in various human applications, including sutures, orthopedics, bone plates and other extended-release medications.

■ Pharmacodynamics

Beyond its opioid-blocking properties, naltrexone has few effects on the human body. Some pupillary constriction is evident with naltrexone, but the mechanism of this effect is unknown. XR-NTX is not associated with the development of tolerance or dependence on naltrexone. However, in individuals who are physiologically dependent on opioids, naltrexone and XR-NTX will precipitate acute withdrawal. This is why individuals must be detoxified from opioids before initiating XR-NTX.

Clinical concerns about the effects of sustained blockade of the μ -opioid receptor on experienced pleasure have led to research investigating whether or not XR-NTX reduces pleasure from activities such as sex, exercise, food and other daily activities. In one report, alcohol-dependent patients ($n = 74$), at the end of receiving XR-NTX injections nearly continuously for

3–5 years were asked to rate how pleasurable a number of daily activities were on a 1 (‘not at all’) to 5 (‘very much’) scale in the prior 90 days [13]. A minority of patients rated drinking alcohol as ‘moderately’, ‘quite a bit’ or ‘very much’ pleasurable, whereas 60–92% rated exercise, sex, eating good food and six other common activities in these categories [13]. Although the study did not assess baseline pleasure ratings or outcomes with opioid-dependent patients, it suggests that the effect of long-term XR-NTX on hedonic response may operate on a gradient, with greater attenuation for alcohol reward than for other rewarding and more healthy stimuli.

Enhanced reactivity to conditioned cues is believed to play an important role in relapse with substance-use disorders. The impact of XR-NTX on such conditioned cues as measured by a blood-oxygen-level-dependent/functional MRI cue-reactivity procedure has been investigated with alcohol-dependent subjects [14]. In this study, the blood-oxygen-level-dependent functional MRI cue-reactivity procedure was conducted immediately before, and 2 weeks after, an XR-NTX or placebo injection. Results indicated that XR-NTX attenuates the salience of cues that have been associated with alcohol. This effect of XR-NTX on brain function may interrupt the process through which conditioned cues can trigger ‘slips’ and relapse. However, the extent to which these results generalized to opioid-dependent individuals is not known.

■ Pharmacokinetics

Following an injection with XR-NTX, there is an initial peak in naltrexone plasma concentrations after approximately 2 h [15]. A second peak occurs approximately 2–3 days later. Concentrations slowly decline 14 days postinjection, but measurable levels persist for more than 1 month. The overall median peak concentration obtained in the pharmacokinetic study was 12.9 ng/ml [15]. Other investigations have indicated that plasma concentrations of naltrexone of less than 1 ng/ml are sufficient to antagonize heroin-induced effects [16,17].

Maximum plasma concentration and the area under the curve for naltrexone and 6- β -naltrexol (the major metabolite of naltrexone) after administration of XR-NTX are proportional to dose [15]. Total naltrexone dose is lower with a single dose of 380 mg XR-NTX compared with oral dosing with 50 mg naltrexone over 28 days (i.e., 1400 mg), but the area under the curve is

three- to fourfold higher [15]. Following the first injection, a steady state is reached at the end of the 1-month dosing interval. Repeat injections of XR-NTX show minimal accumulation (<15%) of naltrexone or 6- β -naltrexol.

Naltrexone is extensively metabolized in humans. Production of the metabolite 6- β -naltrexol is mediated by dihydrodiol dehydrogenase. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6- β -naltrexol and 2-hydroxy-3-methoxy-naltrexone.

Significantly less 6- β -naltrexol is generated with injection of XR-NTX compared with oral administration of naltrexone owing to a reduction in first-pass hepatic metabolism with XR-NTX [15]. Elimination of naltrexone and its metabolites occurs primarily via urine; there is minimal excretion of unchanged naltrexone. The elimination half-life of naltrexone and 6- β -naltrexol following administration of XR-NTX is 5–10 days [15].

Clinical evidence

■ Overview of randomized, placebo-controlled clinical trials

The first evidence of efficacy for a long-acting injectable naltrexone formulation came from a small, short-term (2 month) controlled trial using a product that was not submitted for approval in the USA [18]. This study compared placebo with 192 and 384 mg of long-acting injectable naltrexone to placebo. Retention in treatment was dose related, with 39, 60 and 68% of patients, respectively, remaining in treatment at the end of 2 months. The percentage of urine samples negative for opioids, methadone, cocaine, benzodiazepines and amphetamines was significantly higher for the 384-mg group versus placebo ($p < 0.001$) and for 192 mg versus placebo ($p = 0.046$) when missing urines were considered positive. However, when missing urines were not considered positive, these group comparisons were no longer significant.

The primary efficacy study for the marketed version of XR-NTX was a 6-month placebo-controlled study conducted at 13 clinical sites in Russia [19]. This study is the only published controlled trial of XR-NTX for opioid dependence. The current review therefore focuses on the results of this trial.

Opioid-dependent (primarily heroin) individuals who had completed inpatient opioid detoxification participated. Following detoxification,

XR-NTX was injected every 4 weeks, for a total of six injections over 24 weeks. Patients were randomized to XR-NTX ($n = 126$) or placebo ($n = 124$), with all participants also receiving up to 12 biweekly sessions of individual drug counseling in conjunction with injection visits. The primary efficacy measure was a response profile, defined as the proportion of patients at each possible response level of confirmed opioid-free weeks who achieved that amount (or greater) of opioid-free weeks (using only data from weeks 5 to 24). Weekly confirmed abstinence was defined as the following: the patient provided urine for drug testing, the testing was negative and the patient reported no opioid use. Thus, missing urines were coded as positive for opioids. Patients who used illicit opioids during the trial continued on treatment.

The results of the trial indicated that XR-NTX was statistically and clinically superior to placebo on all *a priori* primary ($p = 0.0002$) (Figure 1) and secondary efficacy measures (Table 1). The median XR-NTX patient had confirmed abstinence for $\geq 90\%$ of weeks versus 35% for placebo and the mean total of confirmed abstinence was 35.7% weeks with XR-NTX versus 22.6% with placebo. There was a greater reduction in opioid craving in the XR-NTX group compared with placebo by week 8 and that difference persisted every week through week 24 ($p < 0.003$). The median number of days retained in treatment was >168 days for the XR-NTX group versus 96 days for the placebo group, with 67 in the XR-NTX group and 47 in the placebo group completing all six injections ($p = 0.017$). XR-NTX patients attended a median of 12 counseling sessions versus eight for placebo patients. The XR-NTX group also improved more than the placebo group with regard to relapse to physiological opioid dependence ($p < 0.0001$), HIV-risk behaviors ($p = 0.025$), self-reported health status ($p = 0.0005$), clinician ratings of global improvement ($p = 0.0002$), and health-related quality of life (mental component; $p = 0.0043$). It should be noted that the absolute levels of improvement in both the XR-NTX and placebo groups occurred in conjunction with the provision of individual drug counseling. Further research is needed to determine the contribution of counseling to the overall degree of improvement evident with XR-NTX.

■ Health economic outcomes

The healthcare costs associated with treatment of opioid dependence with psychosocial treatment

alone, methadone, buprenorphine, oral naltrexone or XR-NTX have been examined using claims data from a large US health plan [20]. In this study, analyses focused on 6-month medication persistence, healthcare utilization, direct paid claims for opioid-dependence medications, detoxification and rehabilitation, opioid-related and nonrelated inpatient admissions, outpatient services and total costs. Although the pharmacy costs for XR-NTX are more than other treatments, total healthcare costs (combining inpatient, outpatient and pharmacy) were found to be greatest with psychosocial treatment alone, and XR-NTX total costs were not significantly different from oral naltrexone or buprenorphine and were 49% lower than with methadone. Although study limitations include retrospective design using case-mix adjustment, lack of indirect costs (e.g., job absenteeism or criminal justice costs) and a focus only on individuals with commercial insurance, XR-NTX-treated patients had fewer opioid-related and nonopioid-related hospitalizations than patients receiving any of the approved oral medications for opioid dependence.

■ Adverse reactions

XR-NTX is generally well tolerated. In the published Phase III clinical trial, two patients in both groups discontinued treatment due to adverse events (drug-dependence relapse, psychotic disorder, hepatitis C and nausea) [19]. Moreover, no overdose events, suicide attempts, deaths or other severe adverse events were reported in the trial. Overall, more patients in the XR-NTX group reported an adverse event than in the placebo group (50 vs 32.3%), but no adverse events were judged to be severe.

Rates of specific adverse events with the use of XR-NTX in an opioid-dependent population were low (Table 2) [21]. Only one adverse event (insomnia) showed a significantly greater incidence for the XR-NTX group compared with placebo (6 vs 1%). Injection-site pain was more prevalent in XR-NTX versus placebo patients (5 vs 1%), and a FDA warning has advised US providers of the occurrence of injection-site reactions and the importance of proper injection technique.

Hepatic enzyme abnormalities were more common with XR-NTX compared with placebo and XR-NTX has a boxed warning regarding naltrexone hepatotoxicity [16]. The Phase III trial sample had a high baseline incidence of

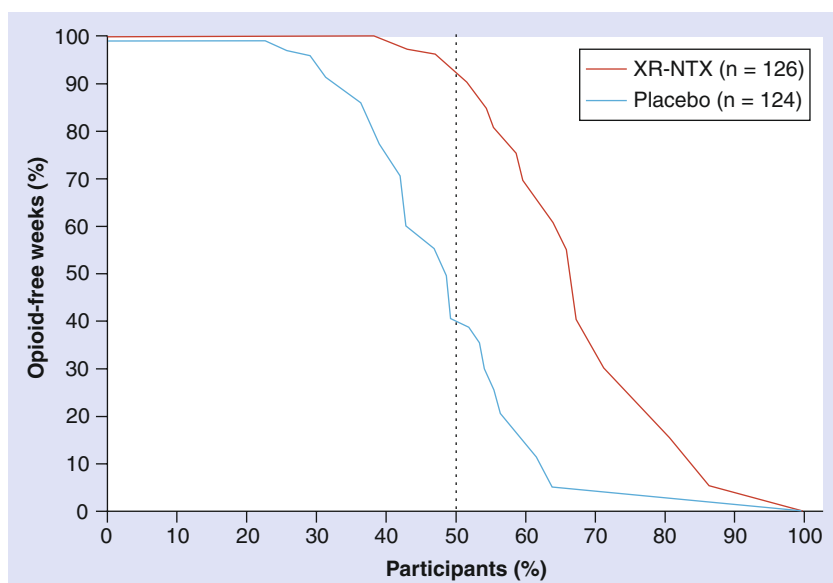


Figure 1. Percentage of confirmed opioid-free weeks (cumulative) among participants treated with extended-release naltrexone versus placebo in the Phase III trial. On this graph, the y-axis represents each decile of possible opioid-free weeks (for the 20-week period of weeks 5–24; the first 4 weeks were excluded to take into account patient testing/opioid use extinction). The x-axis is the percentage of participants who achieved each amount (or greater) of aggregated opioid-free weeks. For example, the percentage of patients who achieved 100% confirmed opioid-free weeks was 23% for placebo versus 36% for XR-NTX; the median placebo patient (vertical dashed line) achieved 35% of opioid-free weeks versus 90% in the XR-NTX group.

XR-NTX: Extended-release naltrexone.

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hepatitis C (89%) and HIV infection (41%); however, abnormal liver function tests over the course of treatment occurred only in patients with existing hepatitis C infections, were transient and not clinically meaningful.

A clinical concern with the use of naltrexone is whether the blockade of μ -opioid receptors is potentially surmountable. There has been one published case report of an individual who overcame the blockade from a surgically implanted version of long-acting naltrexone (approved for use in Russia) by using very large amounts of heroin [22]. In an animal study, rats administered XR-NTX showed no significant respiratory depression or sedation when given hydrocodone or fentanyl at ten- to 20-times the usual doses to achieve an analgesic response [23]. There have been published reports of death from opioid overdose with the implanted version of long-acting naltrexone both during treatment and following removal of the implant [24,25].

Table 1. Efficacy results from a Phase III clinical trial of extended-release naltrexone versus placebo.

Efficacy measure	XR-NTX (n = 126)	Placebo (n = 124)	p-value
Response profile, median proportion (95% CI) of weeks of confirmed abstinence for weeks 5–24	90.0% (69.9–92.4)	35.0% (11.4–63.8)	0.0002
Median (95% CI) self-report of opioid-free days over 24 weeks	99.2% (89.1–99.4)	60.4% (46.2–94.0)	0.0004
Total confirmed abstinence over weeks 5–24 (percent; 95% CI)	45 (35.7%; 27.4–44.1)	28 (22.6%; 15.2–29.9)	0.0224
Craving, VAS score, mean change from baseline (95% CI; scale: 0–100; baseline: XR-NTX 18.2; PBO 21.8)	-10.1 (-12.3 to -7.8)	+0.7 (-3.1–4.4)	<0.0002 [†]
Retention, median number of days (95% CI)	>168 [‡]	96 (63–165)	0.0042 [†]
Treatment completion, number (percent; 95% CI) of patients who completed double-blind treatment period	67 (53.2%; 44.5–61.9)	47 (37.9%; 29.4–46.4)	0.0171
Relapse to physical opioid dependence; number (percent; 95% CI) of participants with positive naloxone challenge test	1 (0.8%; 0.0–2.3)	17 (13.7%; 7.7–19.8)	<0.0001
Risk for AIDS behavior scores; change from baseline, mean (95% CI; scale: 0–1; baseline: XR-NTX 0.300; PBO 0.279)	-0.187 (-0.224 to -0.150)	-0.130 (-0.173 to -0.087)	0.0212
EQ-5D™ General Health State VAS self-ratings; change from baseline, mean (95% CI; scale: 0–100; baseline: XR-NTX 68.7; PBO 69.9)	+14.1 (9.6–18.7)	+2.7 (-1.9–7.8)	0.0005
CGI improvement ratings; percentage of patients rated by investigators as much or very much improved (95% CI)	85.9% (77.8–94.0)	57.5% (45.7–69.5)	0.0002

[†]p-value adjusted for multiplicity.
[‡]Confidence interval could not be calculated because median exceeds study duration.
 CGI: Clinical Global Impression; PBO: Placebo; VAS: Visual analog scale; XR-NTX: Extended-release naltrexone.
 Data taken from [14].

■ Use in special populations

The use of XR-NTX in patients with hepatic impairment deserves comment. A boxed warning in the package insert for oral naltrexone, and subsequently XR-NTX, in relation to hepatotoxicity was prompted by early studies reporting hepatotoxicity at very high dosages of oral naltrexone (350 mg/day) in obese patients and those with senile dementia [26]. To address this concern, a study examined the pharmacokinetics of XR-NTX at the 190-mg dose (although not at the full 380-mg marketed dose) among a small sample of individuals with mild-to-moderate hepatic impairment [27]. Results of the study indicated no difference in pharmacokinetic parameters between those with mild-to-moderate hepatic impairment compared with controls following administration of XR-NTX. Similarly, transient and clinically insignificant enzyme elevations were found but no evidence for hepatotoxicity in a detailed analysis of hepatic safety in the use of XR-NTX for alcohol dependence [28].

The safety, efficacy and pharmacokinetics of XR-NTX in a pediatric population has not been examined to date. The use of XR-NTX during pregnancy, labor and delivery and with nursing mothers, has also not been investigated.

XR-NTX is contraindicated in patients known or expected to have a need for opioid analgesia. Administration of XR-NTX in conjunction with other medications has not been explored in clinical drug interaction studies to date. Prescribers should therefore weigh the risks and benefits of concomitant drug use when considering XR-NTX. However, in the Phase III study of XR-NTX for treatment of alcohol dependence, almost 30% of patients were taking concomitant antidepressants without any evident safety concerns [29].

■ Clinical & practice issues

Although XR-NTX has demonstrated efficacy in a 6-month trial, clinicians will need guidance on how long to continue the injections. This issue remains to be addressed in future studies.

Another key issue for clinical practice is how best to rapidly and safely transition a patient from agonist use to XR-NTX antagonist therapy. Recommendations have been provided for such a transition that tailor the detoxification strategy to the severity of physiological opioid dependence [30]. The suggested approach typically begins with a 4–8 mg dose of buprenorphine, particularly for moderate-to-severely dependent individuals; no buprenorphine may be needed for mildly dependent individuals. This is combined with clonidine and other ancillary medications, followed by 1–2 days of progressive oral naltrexone doses before initiating XR-NTX. Moderately dependent individuals may require partial hospitalization for this regimen and severely dependent individuals may require an inpatient setting. One limitation of this buprenorphine–clonidine–naltrexone procedure is that precipitated withdrawal must be anticipated and actively managed. Furthermore, the efficacy and safety of this approach needs to be investigated in controlled trials. As mentioned, the product labeling for XR-NTX requires that a patient be opioid free for a minimum of 7–10 days.

An alternative method of detoxification involves a gradual taper, first substituting 2–4 mg buprenorphine when withdrawal symptoms emerge, usually 12–18 h after the last dose of heroin or other short-acting opioid, and then titration up to 4–16 mg of buprenorphine per day until withdrawal symptoms are suppressed, then tapering to 0 mg over the next 7–14 days. This would then be followed by the appropriate opioid-free period before initiating XR-NTX [30].

A further consideration in the use of XR-NTX is pain management. Two options are regional analgesia and use of nonopioid analgesics. If possible, a patient can schedule surgery after discontinuing XR-NTX. Because the blockade of μ -opioid receptors by naltrexone is competitive, it is surmountable. Thus, opioid pain therapy can be implemented as part of anesthesia or analgesia. However, if opioids are used, the patient needs to be continuously monitored in an anesthesia care setting by persons not involved

Table 2. Adverse events in the extended-release naltrexone Phase III trial.

Adverse events	XR-NTX 380 mg; n = 126; n (%)	Placebo; n = 124; n (%)
Nasopharyngitis	9 (7)	3 (2)
Insomnia	8 (6) [†]	1 (1)
Hypertension	6 (5)	4 (3)
Influenza	6 (5)	5 (4)
Injection-site pain	6 (5)	1 (1)
Toothache	5 (4)	2 (2)
Headache	4 (3)	3 (2)

[†]p < 0.05 different from placebo.
Data taken from [16].

in the conduct of the surgical or diagnostic procedure. The healthcare professional providing the opioid therapy should be trained in the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation and the setting equipped and staffed for cardiopulmonary resuscitation.

Although the challenges of successful transition from agonist use and pain management are important clinical issues, the approaches to these challenges described above have been met with success in routine practice [30,31]. In addition, these challenges are not dissimilar to those evident with the use of short-acting opioid antagonists. These challenges also have to be weighed in the context of a once-monthly treatment for prevention of relapse in opioid-dependent individuals that is free of physical dependence, addresses the compliance of oral medications and is not subject to illegal diversion. XR-NTX represents a distinct alternative to previously existing treatment options for eligible patients.

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