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Extended-release injectable naltrexone for opioid use disorder: A systematic review

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Abstract

Aims—To review systematically the published literature on extended-release naltrexone (XR-NTX, Vivitrol®), marketed as a once-per-month injection product to treat opioid use disorder. We addressed the following questions: (1) How successful is induction on XR-NTX?; (2) What are adherence rates to XR-NTX?; and (3) Does XR-NTX decrease opioid use? Factors associated with these outcomes as well as overdose rates were examined.

Methods—We searched PubMed and used Google Scholar for forward citation searches of peer-reviewed articles from January 2006 to June 2017. Studies that included individuals seeking treatment for opioid use disorder who were offered XR-NTX were included.

Results—We identified and included 34 studies. Pooled estimates showed that XR-NTX induction success was lower in studies that included individuals that required opioid detoxification

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Conflicts of Interest: BPJ, AFH, SS, EAO, and GEB have no conflicts of interest to declare.

AUTHOR'S CONTRIBUTIONS

BPJ, AFH, GEB, and KS conceived the review strategy and organization. BPJ, AFH, SS, and EAO performed the literature search and data extraction. BPJ wrote the first draft of the manuscript. DAT provided clinical expertise and input. All authors made substantial contributions to and approved of the final manuscript.

(62.6% [95% CI: 54.5% – 70.0%]) compared with studies that included individuals already detoxified from opioids (85.0% [95% CI: 78.0% – 90.1%]). 44.2% (95% CI: 33.1% – 55.9%) of individuals took all scheduled injections of XR-NTX, which were usually 6 or less. Adherence was higher in prospective investigational studies (i.e., studies conducted in a research context according to a study protocol) compared to retrospective studies of medical records taken from routine care (6-month rates: 46.7% [95% CI: 34.5% – 59.2%] vs. 10.5% [95% CI: 4.6%–22.4%], respectively). Compared with referral to treatment, XR-NTX reduced opioid use in adults under criminal justice supervision and when administered to inmates before release. XR-NTX reduced opioid use compared with placebo in Russian adults, but this effect was confounded by differential retention between study groups. XR-NTX showed similar efficacy to buprenorphine when randomization occurred after detoxification but was inferior to buprenorphine when randomization occurred prior to detoxification.

Conclusions—Many individuals intending to start extended-release naltrexone (XR-NTX) do not and most who do start XR-NTX discontinue treatment prematurely, two factors that limit its clinical utility significantly. XR-NTX appears to decrease opioid use but there are few experimental demonstrations of this effect.

Keywords

opioid use disorder; medication-assisted treatment; heroin; prescription opioids; naltrexone; extended-release; injectable

INTRODUCTION

Opioid misuse and dependence is a significant global disease burden that varies geographically (1). In the United States, overdose deaths and the prevalence of opioid use disorder (OUD) from prescription opioids, heroin, and illicitly manufactured synthetic opioids have increased dramatically in the past two decades (2–4). This epidemic has prompted actions to expand funding and access to treatment services (5, 6), including medication-assisted treatment (MAT) that many individuals could benefit from though rarely receive (7). Three MATs are approved by the Food and Drug Administration (FDA) for OUD in the United States (8). Their therapeutic effects are mediated primarily through the μ-opioid receptor and include the full agonist methadone, the partial agonist buprenorphine, and the full antagonist naltrexone (9). Any licensed provider (e.g., physician, nurse practitioner) can prescribe naltrexone, whereas buprenorphine requires special training and carries limits on the number of patients each provider can treat (10). Methadone is more regulated and only dispensed by certified opioid treatment programs (11).

Decades of research show that methadone and buprenorphine can reduce opioid use and increase treatment retention (12, 13), and both are listed as essential medicines by the World Health Organization (14). In contrast, there is limited evidence that oral naltrexone promotes opioid abstinence and treatment retention, despite being available and approved to treat OUD since 1984. A systematic review of 13 studies involving 1,158 participants (15) found no significant differences on these outcomes for participants offered oral naltrexone compared to placebo and to no-medication controls. The authors concluded that the studies did not permit an adequate evaluation of oral naltrexone’s effects for OUD treatment.

The inability to properly evaluate oral naltrexone was due to poor adherence – fewer than one-third of participants who began taking oral naltrexone continued through the end of treatment, which averaged 6 months. When participants adhere to oral naltrexone at higher rates, such as those produced by contingency management interventions (16), the effects on opioid use are significant (17). However, in the absence of specialized interventions, problems related to adherence reduce the effectiveness of naltrexone. Thus, its use has been limited to highly motivated populations (18, 19).

To improve adherence and naltrexone's clinical potential for treating OUD, extended-release injectable and surgically implantable formulations have been developed and evaluated in several countries (20). Whereas oral naltrexone must be taken at least three times per week, one dose of these longer-acting formulations can deliver therapeutic levels of naltrexone that last from 1 to 7 months. The increased duration of exposure to naltrexone in one implantable formulation has been shown to decrease overdose risk associated with poor adherence to oral naltrexone (21). Unlike methadone and buprenorphine, however, naltrexone is contraindicated for individuals with current physiological dependence on opioids because its use in these individuals can precipitate severe withdrawal (22). Therefore, it is recommended that individuals be abstinent from all opioids for at least 7–10 days before receiving their first dose.

Multiple longer-acting formulations have been tested (23, 24) but only one is approved by the FDA for OUD (approved in 2010 and marketed as Vivitrol®, hereafter referred to as XR-NTX) (25, 26). XR-NTX contains 380mg naltrexone delivered as an intramuscular gluteal injection and is well-tolerated with mild side effects (e.g., headache, injection site soreness) (27, 28). Dosing occurs monthly and blocks the subjective, reinforcing, and physiological effects of opioids (29). Relative to methadone and buprenorphine, there are a limited number of studies on XR-NTX for OUD. The most recent review of XR-NTX's therapeutic efficacy for OUD from 2013 (26) included five studies, two of which were conference presentations. In recent years, however, many prospective and retrospective studies on XR-NTX for OUD have been completed and published.

In the present review, we provide a systematic and comprehensive update of studies evaluating XR-NTX for OUD and address the following primary questions: (1) How successful is induction on XR-NTX?; (2) What are adherence rates to XR-NTX?; (3) Does XR-NTX decrease opioid use?; and (4) What are the factors associated with induction on and adherence to XR-NTX and opioid use during XR-NTX treatment? We also examined reports of overdose deaths, which previously have been reviewed for oral and implantable naltrexone formulations but not XR-NTX.

METHODS

We followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (30) and pre-registered the protocol in PROSPERO (CRD42016036755).

Search strategy

We performed a systematic review of the literature using PubMed. Studies that were written in English, were conducted in humans, contained the word string "naltrexon*" in the title or abstract, included "opioid related disorders" as a MeSH heading, and were published beginning in 2006 were considered (See supplemental materials for full search syntax). We chose this date because it was the year in which the first outpatient randomized controlled trial using injectable naltrexone for OUD was published (31). We reviewed the references of all relevant studies and used Google Scholar for forward citation searching to identify additional studies.

Inclusion criteria

Studies that met the following criteria were included: (1) the study was peer-reviewed; (2) participants were seeking treatment for opioid use or met criteria for opioid abuse, opioid dependence, or OUD; (3) one or more injections of XR-NTX were offered; (4) XR-NTX was the FDA-approved formulation (Vivitrol®); (5) the study was not exclusively in-patient; and (6) the study reported outcomes or predictors of XR-NTX induction, adherence, or its effects on opioid use. We chose to exclude studies using injectable or implantable formulations of naltrexone not approved by the FDA (e.g., Depotrex®) to focus our findings on the formulation currently used in practice in the United States, because these other formulations have been recently reviewed (23, 24), and because little new research has been published on their effects. Studies that were exclusively in-patient could be included if they reported induction as an outcome (e.g., in-patient detoxification and induction evaluations). There were no restrictions related to study design, population, or comparator (if included).

Outcomes

The primary outcomes were (1) rate of induction on XR-NTX, defined as the percentage of participants enrolled in a study offering XR-NTX who received their first injection; (2) adherence to XR-NTX, defined as the percentage of participants receiving each injection; and (3) opioid use, defined as the percentage of urine samples negative for opioids. Not all studies included in this review used these outcome definitions. Variations and different definitions are noted for individual studies. Overdose outcomes were simple counts and percentages.

Data extraction

We used a standardized template to extract data from each study, which included general information (e.g., year, setting) and methods (e.g., design, duration) and methods and results specific to each outcome (e.g., for induction – if a formal detoxification was included, description of induction protocols, induction success rate, reasons for failures).

Review methods, quality assessments, and data synthesis

Study selection was performed independently by two authors. The standardized template was pre-piloted independently by two authors, and the first author extracted all relevant data for the review. Disagreements in study selection and issues related to data extraction were resolved by discussion among the authors. Two authors independently evaluated quality

assessments for each study and for each outcome within a study and reached consensus by discussion. The Cochrane Collaboration's tool (32) was used for randomized controlled trials (RCTs), the Downs and Black checklist for non-randomized studies (33), and the Newcastle-Ottawa quality assessment scale for cohort studies (34).

Rates of induction on and adherence to XR-NTX were pooled statistically using an inverse variance random-effects model (35) to account for significant heterogeneity across studies. Post-hoc analyses of subgroups identified during the review process were also performed. Meta-analytic approaches were not pursued for opioid use outcomes as there were too few studies (≤ 2) that isolated the effects of XR-NTX on opioid use using the same comparator. Throughout the review, we use a structured narrative format to synthesize the literature, organized by research question and study design. In general, prospective study designs were investigational studies conducted in a research context according to a study protocol, whereas retrospective study designs were chart and other medical record reviews taken from routine clinical care settings.

RESULTS

Included studies

A total of 270 studies were assessed for eligibility. We included 34 studies that reported outcomes on XR-NTX induction (n = 17), adherence (n = 24), or opioid use (n = 25). Fifteen studies reported overdose outcomes. While revising the manuscript, two large comparative effectiveness trials (36, 37) of XR-NTX were published and added to this review. Results from the study selection process are shown in Figure 1, and general study characteristics are shown in Table 1.

Quality assessments

Quality ratings are shown in Table 2. Twelve studies were RCTs, six of which were designed specifically to evaluate XR-NTX versus a control; twelve were non-randomized studies; and six were cohort studies. RCTs were generally of low risk across categories and outcomes. Nearly all RCTs offered XR-NTX as open-label, which introduced potential bias for adherence and opioid use outcomes. Assessment blinding was rarely reported and its impact on bias was unclear. Quality ratings for non-randomized studies varied, with most studies having low external validity, moderate bias, and moderate to significant confounding. The cohort studies were well-designed and had few poor-quality indicators. One study (38) failed to control for confounding participant factors and definitions of opioid abstinence were unclear in two studies (39, 40).

Induction on XR-NTX

Prospective studies—Fifteen prospective studies reported outcomes on XR-NTX induction (Table 3). Five (28, 37, 38, 41, 42) required opioid abstinence at the outset, and one (43) did not require opioid abstinence but recruited recently incarcerated participants who were nearly all abstinent upon release from jail or prison. The nine remaining studies (36, 44–51) included individuals who were actively using opioids and required detoxification.

We identified several procedures for detoxifying and inducting individuals on XR-NTX. One research group (44, 45) used a rapid 7–8 day inpatient procedure, which they later expanded to an outpatient setting (50). The protocol involved a brief buprenorphine stabilization followed by a washout and gradually increasing doses of oral naltrexone for 3 to 4 days. A small pilot study (47) evaluated a slightly different rapid 8-day procedure delivered in an outpatient setting that began with 3 days of very low dose oral naltrexone (i.e., < 1mg) combined with buprenorphine. Thereafter, buprenorphine was stopped and oral naltrexone increased over 4 days. In both rapid induction protocols, withdrawal was managed with non-opioid medications (e.g., clonidine, trazodone, zolpidem). Another procedure (46, 51) occurred in a specialized outpatient employment-based drug treatment center (52), lasted 1 to 4 weeks, and used a form of contingency management (i.e., employment-based reinforcement). Financial incentives were used to promote opioid abstinence (for participants with recent use) and oral naltrexone adherence. Participants who provided opioid-negative urine samples and/or adhered to staff-observed oral naltrexone doses could earn wages for working in a therapeutic workplace.

Rates of XR-NTX induction ranged from 33% to 72% for studies that included individuals requiring opioid detoxification (Figure 2). Overall, studies that targeted individuals requiring detoxification had lower induction rates than studies that did not require detoxification (pooled estimate [95% CI] = 62.6% [54.5%–70.0%] vs. 85.0% [78.0%–90.1%]). Common reasons for failing to initiate XR-NTX were failing to complete the detoxification (if included), relapse, being lost to follow-up, and declining the medication (Supplemental Table 1). One pilot study (49) compared medication initiation rates between individuals requiring detoxification who were randomized to XR-NTX or treatment as usual (i.e., buprenorphine or methadone). Induction on XR-NTX was significantly lower than on buprenorphine or methadone (41.7% vs. 100%). A larger trial (36) reported similar findings that induction was significantly lower for participants randomized to receive XR-NTX versus buprenorphine (72.1% vs. 94.1%). Among patients who are already detoxified, rates of induction for patients randomized to receive XR-NTX or buprenorphine were similar (88.9% and 91.1%, respectively) (37).

Retrospective studies—Only one retrospective study reported XR-NTX induction outcomes (53). Data were gathered from 7,687 privately insured, opioid-dependent individuals receiving treatment in residential programs. Just 8% of patients were recommended for XR-NTX. Among those recommended for XR-NTX, fewer than one-third (28.1%; 168/598) received their first injection. For unknown reasons, many participants (31.6%) changed their minds about taking XR-NTX. Others were unable to pay for the medication (20.7%; usually due to insurance denial), discharged early (28.1%), or left against medical advice (15.6%).

Factors associated with induction—Four studies (42, 45, 46, 50) experimentally investigated whether adjunctive medication, detox-type, or induction contingencies and setting impacted XR-NTX induction, and four studies (45, 50, 51, 54) examined baseline predictors of XR-NTX induction. Adding dronabinol (a cannabinoid-1 partial agonist) to an 8-day inpatient rapid detox did not significantly improve induction rates compared to

placebo (66% vs. 55%). Although statistical tests were not reported, participants receiving employment-based contingency management for adherence to XR-NTX had higher induction rates than those whose adherence was not contingent on accepting XR-NTX (100% vs. 84.2%) (46). Only one study (50) experimentally evaluated different induction procedures and showed that individuals undergoing a 7-day outpatient naltrexone-assisted detox followed by XR-NTX on Day 8 were nearly 3 times more likely to be inducted than those receiving a 7-day outpatient buprenorphine-assisted detox followed by a 7-day washout period (XR-NTX on Day 15). A small pilot study (42) among adult inmates showed that those randomized to receive XR-NTX prior to release had higher rates of induction than those referred to the community to be inducted after release. This finding was also observed in one prospective natural experiment study (38).

An analysis of 29 patient demographics receiving a 7-day rapid inpatient detox (54) found that only two measures were associated with success. Patients who were older and used fewer opioids daily were more likely to complete the detox. Among participants receiving outpatient detox and XR-NTX induction, success was higher for prescription opioid users than heroin users but did not differ by route of opioid use or daily opioid use amount (50). Within a sample of opioid users with marijuana use histories, pre-enrollment marijuana use did predict successful induction (45). Finally, in an outpatient contingency management procedure, participants who had recently completed a long-term detox (≥ 21 days) and who were not on parole or probation were more likely to complete the induction than those who completed a shorter-term detox (<21 days) or who were on parole or probation (51).

Adherence to XR-NTX

Prospective studies—Sixteen prospective studies reported outcomes on adherence to XR-NTX (27, 28, 36–38, 41, 42, 44–46, 48–50, 55–57) (Table 4), which was usually evaluated for six injections or less (87.5%; 13/16 studies). Adherence rates varied but generally decreased over time. The highest drop-off in adherence rates occurred early in treatment, usually between participants' first and second injection (Figure 3). Rates of perfect adherence through six months among participants who started XR-NTX ranged from 15%–74% (pooled estimate [95% CI] = 46.7% [34.5%–59.2%]. Longer adherence rates (13 and 19 months) were reported in a study from Russia (56), which showed that individuals who completed 6 months of XR-NTX or placebo treatment in a previous study (27) adhered continuously the following year at rates of 58.2% and 68.1%, respectively (31.0% and 25.8% of the original samples, respectively). A long-term United States study with healthcare professionals found that 12- and 24-month adherence rates were 55.3% and 36.8% (57). The only placebo-controlled study (27) showed that adherence was higher to XR-NTX than placebo (57.9% vs. 41.9%). A recent pilot study (49) compared adherence to XR-NTX and treatment as usual (buprenorphine/methadone). Rates of adherence were higher among those who started XR-NTX (5/5: 100%) than buprenorphine or methadone (6/12: 50%). In much larger trials, adherence rates for individuals who start XR-NTX have recently been shown to be similar to those for buprenorphine through 3 (37) (XR-NTX: 78.9% vs. buprenorphine: 68.1%) and 6 months (36) (XR-NTX: 47.1% vs. buprenorphine: 42.6%).

Retrospective studies

Seven retrospective studies reported adherence outcomes (22, 58–63) (Table 4). Observation periods were generally around 6 months long. The decline in adherence rates over time varied, but were less than 50% by the third injection (pooled estimate [95% CI] = 46.3% [27.0%–66.7%]; Figure 3). Fewer than 10% of participants adhered to XR-NTX through their sixth injection (pooled estimate [95% CI] = 10.5% [4.6%–22.4%]. A follow-up study (63) of respondents who enrolled in an XR-NTX clinical study (50) showed that 12% were in XR-NTX treatment at the time of the survey (21 months on average after study completion) and 26% received at least one XR-NTX injection after the intervention ended.

One study (58) compared XR-NTX adherence to oral NTX, buprenorphine, and methadone among a sample of privately insured patients receiving treatment from 2005–2009 (prior to XR-NTX's FDA-approval for OUD). A higher percentage of patients receiving XR-NTX (21%) had medication possession ratios (i.e., ratio of days' supply of the medication to total days in the observation period) ≥ 0.8 compared to patients receiving oral NTX (8%). Patients receiving methadone (29%) did not differ from those receiving XR-NTX on this outcome but patients receiving buprenorphine had higher rates (34%). There were no group differences based on mean number of persistent days with medication. Among adolescents, one study showed that rates of adherence to XR-NTX and buprenorphine were similar across 6 months of treatment (62).

Factors associated with adherence

Five studies experimentally evaluated methods to improve XR-NTX adherence (Supplemental Figure 1). Compared to placebo, adding dronabinol to XR-NTX treatment had no significant effect on adherence (45), whereas adding memantine produced significantly lower treatment retention and adherence (44). In contrast, employment-based reinforcement for XR-NTX adherence promoted significantly higher rates of adherence. Six-month adherence rates for participants receiving employment-based reinforcement for XR-NTX adherence (73.7%) were tied with those seen in US healthcare professionals for the highest of any study or subgroup. Among participants who initiated XR-NTX, those who had received naltrexone-assisted detox immediately received their second injection of XR-NTX (89.1%) at similar rates as those who received a buprenorphine-assisted detox followed by a 7-day washout (82.4%) (50). Finally, incarcerated participants who initiated XR-NTX prior to release had higher adherence than those who were referred to XR-NTX treatment in the community, though this effect disappeared over time (42).

Eight studies (44, 45, 48, 50, 55, 60, 61, 64) reported whether a variety of participant factors (e.g., demographics, drug use) were associated with XR-NTX adherence (Supplemental Table 2). Some variables were related to adherence but many of the associations were inconsistent across studies or reported only by one study. Thirteen studies (22, 27, 28, 36, 37, 41, 44, 46, 48, 55–57, 63) provided some information on reasons for non-adherence after beginning XR-NTX, which included losing contact with participants (e.g., treatment drop out, loss to follow-up, incarceration), adverse events, and other personal reasons (see Supplemental Table 1).

XR-NTX and opioid use

The duration of XR-NTX (1 to 24 months), opioid use outcome measures, and methods of handling missing data varied considerably across the prospective studies. Given this heterogeneity, detailed findings are reported for individual studies in Table 5. Sixteen prospective studies offered at least one injection of XR-NTX and reported opioid use outcomes.

Prospective studies that *did* experimentally isolate the effects of XR-NTX on opioid use (i.e., RCTs)—Six studies evaluated the effects of XR-NTX on opioid use. Two pilot studies (41, 49) and one larger study (28) compared XR-NTX to treatment referral controls, one study (27) compared XR-NTX to placebo, and two studies compared XR-NTX to buprenorphine with randomization occurring before (36) or after (37) opioid detoxification was completed (Table 5). Two of the three studies that compared XR-NTX to treatment referral controls found that XR-NTX produced superior opioid use outcomes (one study did not test for group differences). The pivotal placebo-controlled study (27) also reported better opioid use outcomes but did not demonstrate an effect of XR-NTX on opioid use independent of treatment retention. When randomization occurred after opioid detoxification, XR-NTX was found to be non-inferior to buprenorphine (37). However, when randomization to XR-NTX and buprenorphine took place prior to opioid detoxification, participants assigned to receive buprenorphine had significantly better opioid use outcomes, an effect that was attributed to XR-NTX's induction hurdle and subsequent relapse among induction failures (36).

Prospective studies that did *not* experimentally isolate the effects of XR-NTX on opioid use—Ten studies offered open-label use of XR-NTX using no controlled comparator with (42, 44–46, 50) or without (47, 48, 55–57) randomized evaluations of induction protocols or adjunctive treatments (Table 5).

Retrospective studies—Six retrospective studies (Table 5) reported outcomes on opioid use, three of which compared the effects of XR-NTX to other MATs or no medication controls (39, 40, 62). Among parolees and probationers, opioid use outcomes observed in XR-NTX recipients were similar to those receiving oral naltrexone but better than both buprenorphine and psychosocial treatment only (39). No differences in opioid use were observed between these medications in a similar study using a community sample (40) or among adolescents receiving XR-NTX or buprenorphine (62). Three other studies, one in adolescents (22), one in dually diagnosed individuals (59), and one in individuals who had completed an XR-NTX clinical study (63) reported outcomes of receiving XR-NTX with no control, to a pre-XR-NTX period, or as a function of past XR-NTX adherence (see Table 5).

Factors associated with XR-NTX and opioid use—Eight studies reported correlational or experimental analyses of predictors of XR-NTX's effect on opioid use. A secondary analysis (65) of the pivotal placebo-controlled study (27) showed that none of the 25 baseline factors predicted a positive clinical response to XR-NTX. Two secondary analyses (66, 67) of a large United States study comparing XR-NTX to treatment referral (28) found that XR-NTX induction setting interacted with opioid relapse and that of 36

baseline factors only alcohol use to intoxication moderated the treatment effect. Specifically, because relapse was higher among patients who received XR-NTX during a short-term inpatient stay, its protective effects were greater than those who received XR-NTX during long-term inpatient stays and in outpatient settings. However, the effect of induction setting was only significant in the short-term (5 weeks; not significant at 26 weeks). XR-NTX was more likely to prevent relapse in participants who did not report drinking to intoxication 30 days before randomization.

Two recent studies showed that education level and subscales on the Addiction Severity Index (48) and daily opioid amount, type of opioid use (heroin vs. prescription opioids), and route of administration (50) were not predictive of opioid urine outcomes. Further, adding dronabinol (45), memantine (44), or employment-based reinforcement for XR-NTX adherence (46) did not significantly improve opioid use outcomes.

XR-NTX and overdose

Of the 22 studies that reported original opioid use outcomes (i.e., not secondary analyses), 12 prospective and 3 retrospective studies reported data on overdose associated with XR-NTX (see Supplemental Table 3). Methods of monitoring overdose outcomes varied. One small pilot study audited the National Death Index (41), whereas the majority recorded adverse events at study visits or did not provide details on how overdose events were determined. In 60% (9/15) of the studies, there were no reported overdose events among individuals assigned to receive XR-NTX. In the six studies where overdoses (nonfatal and/or fatal) were reported, nonfatal overdose death rates were 3.5% (2/57), 4.0% (1/25), and 5.3% (15/283); fatal overdose death rates were 0.7% (1/150), 0.7% (2/283),1.2% (2/171), and 4.5% (3/67). No studies were powered to detect significant differences in overdose between XR-NTX and any comparators.

DISCUSSION

Since a previous review in 2013 (26), 29 studies have been published that report original investigations of XR-NTX in populations with OUD. In this systematic review, we present an up-to-date and comprehensive synthesis of the published literature on XR-NTX to treat OUD. We examined whether XR-NTX decreases opioid use but also reported two outcomes critical to its success – starting and continuing to take the medication. We also explored what patient and intervention factors predicted greater induction, adherence, and treatment response, and examined rates of overdose in published studies. There was considerable heterogeneity in the study designs, outcomes, and findings, but we offer the following general conclusions and recommendations for future research.

Induction on XR-NTX

Most participants started XR-NTX in studies focusing on individuals who were already detoxified from opioids; however, for those requiring detoxification, roughly 40% did not start XR-NTX. This result suggests that XR-NTX induction is likely to be high among patients who achieve initial opioid abstinence. XR-NTX may be the most appealing medication option for these individuals, who may be reluctant to start treatment with

methadone or buprenorphine. Although detoxified patients had more success starting XR-NTX, evidence of this outside the context of investigational studies, which were usually conducted in academic medical settings, is limited. Only one study (53) reported induction outcomes among detoxified patients in routine care, in which fewer than one-third recommended for XR-NTX started it. Practical issues not inherent in investigational studies may explain this discrepancy and pose additional constraints on starting XR-NTX and include the timing of medication ordering, storage, and delivery before discharge; covering the high cost of XR-NTX and negotiating insurance coverage; and ensuring patients will have access to continuing XR-NTX treatment after initiation (68).

Few individuals seeking treatment will have achieved the 7–10 days of opioid abstinence to start XR-NTX recommended in the manufacturer's medication packet insert. There is no agreed-upon detoxification and XR-NTX induction protocol, but rapid week-long procedures that involve brief buprenorphine and increasing low-dose naltrexone accompanied by non-opioid medications to manage withdrawal discomfort (44, 45, 47) have been the most commonly evaluated approaches. These methods may be superior to detoxification with buprenorphine-alone (50) and could be implemented in outpatient settings where most patients receive treatment (69), but may require significant changes to the outpatient treatment of OUD (e.g., use a compounding pharmacy, open 7 days per week). A major advantage of XR-NTX is that it is not regulated like methadone or buprenorphine, and providers do not have to complete specialized waivers to prescribe it. Critical questions are whether providers – some of whom may have limited or no training in treating OUD – will be able to easily and safely manage patients through the induction protocols, be willing to treat these individuals, and have appropriate training and support to feel comfortable administering the injections (70).

The induction hurdle for individuals requiring detoxification limits the clinical utility of XR-NTX treatment significantly. Future research should experimentally investigate novel methods to rapidly detoxify and induct patients on XR-NTX with greater success, and assessments of the feasibility and induction rate of these protocols in routine care will be needed. In addition, studies should continue to explore patient-level factors that may predict successfully starting XR-NTX. Some behaviors characteristic of less severe opioid use (i.e., using less (54), using primarily prescription opioids (50), being able to complete a long-term detox (51)) may be associated with better outcomes, but these findings need to be replicated.

Adherence to XR-NTX

Adherence rates decreased over time, with 47% of participants who started XR-NTX still adhering at the latest time point, which averaged less than 6 months. Prospective investigational studies conducted in a research context according to study protocols reported much higher adherence rates over time compared to retrospective medical record review studies taken from routine clinical care settings. The reasons for this large divergence are unclear but may include differences between samples owing to study exclusion criteria (71, 72) and a host of procedural differences between investigational studies and routine clinical care (e.g., study compensation, medication cost, follow-up efforts, expertise and familiarity with XR-NTX, contact with healthcare staff) (73). The observed difference in adherence

between these two types of studies should be interpreted cautiously, however. The comparison was not controlled, and there were just four retrospective studies included.

We chose to report adherence rates based on individuals who initiated XR-NTX treatment and received their first injection. An alternative approach in which XR-NTX induction failures are included produces considerably lower adherence rates. Twelve prospective trials reported outcomes for both induction and adherence (28, 36–38, 41, 42, 44–46, 48–50). In these studies, pooled adherence estimates at the last time point, which averaged 4 months, was 59.0% (95% CI: 46.3%–70.6%) among those who initiated XR-NTX but decreased to 41.2% (95% CI: 31.9%–51.3%) when using an intent-to-treat approach among all individuals intending to start XR-NTX.

Offering incentives for accepting XR-NTX was the only intervention that increased long-term adherence (46). Despite nearly tripling 6-month adherence to XR-NTX, this intervention had only a small effect on reducing opiate use and is unlikely to be adopted in most treatment settings. There may be patient characteristics that clinicians can identify to predict who will remain engaged in long-term XR-NTX treatment but none were particularly robust and replicated across studies.

The evidence to evaluate XR-NTX adherence versus buprenorphine and methadone was inconsistent, with studies showing lower, similar, and higher XR-NTX adherence (36, 37, 49, 58, 62). Two recent comparative effectiveness trials (36, 37) suggest that once initiated, rates of adherence to XR-NTX and buprenorphine are similar. However, in the Norwegian trial, buprenorphine was given daily in a controlled environment, which is not the standard delivery method in other countries (e.g., United States) and may have imposed additional barriers to adherence. Although the need to improve treatment retention is not unique to XR-NTX, the resources needed to completely detoxify and induct individuals on XR-NTX are substantial and would be required again after a relapse to resume XR-NTX, an issue not faced by buprenorphine or methadone treatment.

Because the effects of XR-NTX on opioid use have been shown not to persist once discontinued (28), future research should include longer measures of adherence, particularly in real-world settings. An industry-sponsored multi-center patient registry study of XR-NTX for OUD involving over 400 patients was completed but the results have not been published (NCT01422837). Even with the improved long-acting formulation, most patients starting XR-NTX will need additional support and interventions to promote continued adherence. Researchers should evaluate innovative pharmacotherapies and behavioral interventions to keep patients engaged in XR-NTX treatment and identify characteristics of patients who remain on XR-NTX.

XR-NTX and opioid use

We documented an increase in the number of published studies on XR-NTX for OUD in the past several years that show XR-NTX can decrease opioid use. However, of the 22 investigational studies that reported opioid use outcomes in this review, only 6 were randomized studies that isolated the effects of XR-NTX, and 2 of these were small pilot studies. The original pivotal study conducted in Russia and published in 2011 (27) showed

that XR-NTX increased treatment retention relative to placebo. However, its effect on opioid abstinence was not independently demonstrated because urine sample collection rates differed between groups and the only analysis reported assumed missing samples were positive for opioids. In contrast, a 2016 United States study among adults involved in the criminal justice system (28) provided rigorous evidence that XR-NTX reduces opioid use relative to a treatment referral condition.

The recent randomized trials in Norway (37) and the United States (36) are the first to compare the relative effectiveness of XR-NTX to buprenorphine, a gold standard OUD treatment. The Norwegian trial was brief (3 months), buprenorphine dosing occurred in a controlled environment, and the buprenorphine dose was low (11.2 mg). The United States trial recruited participants from inpatient detoxification centers, which may have favored XR-NTX induction and contributed to the high induction success (72%; the highest among studies for individuals requiring a detoxification). These limitations notwithstanding, the trials showed that XR-NTX and buprenorphine can produce similar short-term opioid outcomes. Critically, this finding was only true when considering individuals who had successfully completed an opioid detoxification. When induction failures (who typically progressed to relapse) were included, XR-NTX was less effective than buprenorphine in improving opioid use outcomes. This occurred despite the very high induction success rates in this study. As with XR-NTX induction and adherence, more work should identify patient factors associated with a positive response to XR-NTX's effects on opioid use.

XR-NTX and overdose

The number of participants experiencing overdose in the reviewed studies was low, but most studies did not report clearly how overdose events were measured, particularly among participants who were lost to follow-up. The predominant method was to collect adverse event information at weekly or monthly study visits. Given the high dropout rates observed in the reviewed studies and the known overdose risks of stopping agonist treatment (74), it is critical that future studies and real-world evaluations more rigorously evaluate and report fatal and nonfatal overdoses. The extent to which XR-NTX induction failures may contribute to overdose risk is also unknown and requires further study.

CONCLUSION

XR-NTX could play an important role in curbing the opioid epidemic but several issues and concerns exist regarding its efficacy and effectiveness in real-world settings. Many individuals intending to start XR-NTX do not, and most who do start XR-NTX discontinue treatment prematurely. XR-NTX appears to decrease opioid use but there are few experimental demonstrations of this effect in the literature. The barriers faced in completing XR-NTX induction significantly limit its clinical utility and impact when compared to buprenorphine. Future work should develop methods of successfully detoxifying and inducting individuals on XR-NTX, design interventions and treatment approaches to increase long-term adherence, and more comprehensively evaluate overdose risks associated with XR-NTX treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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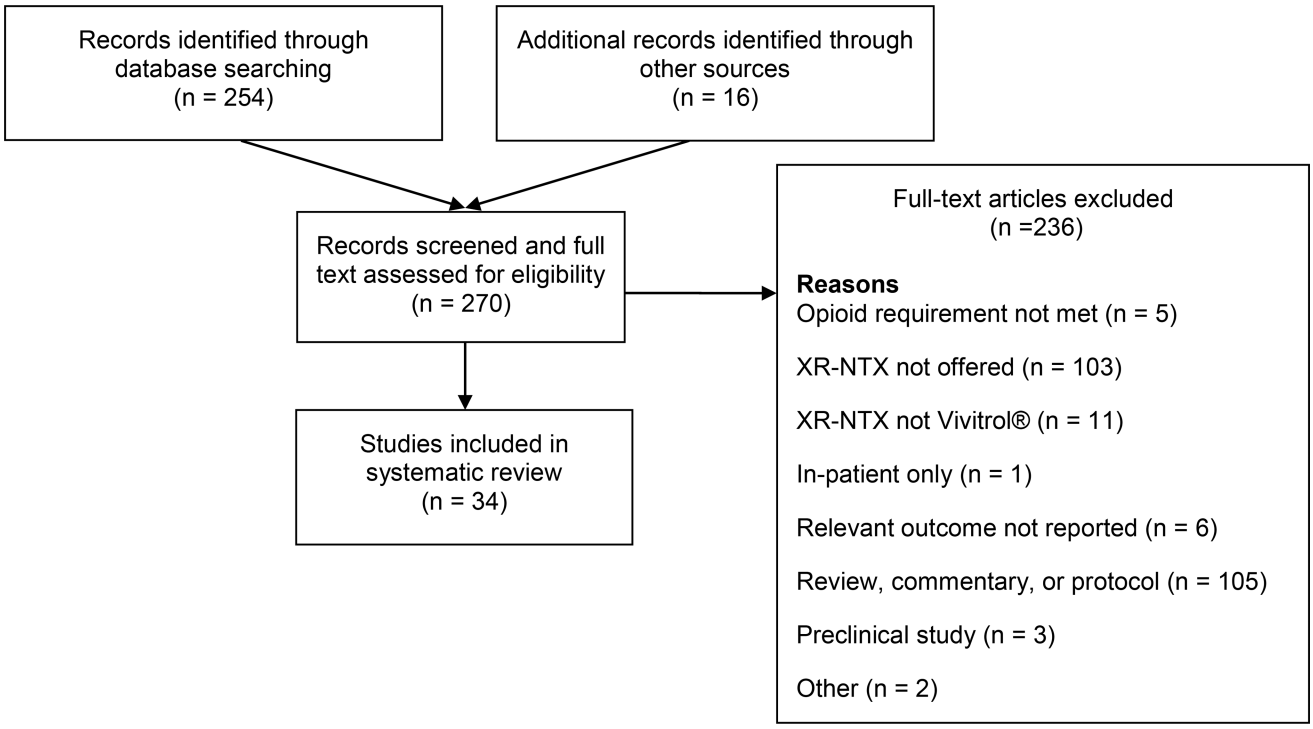


Figure 1.
PRISMA flow diagram of study selection

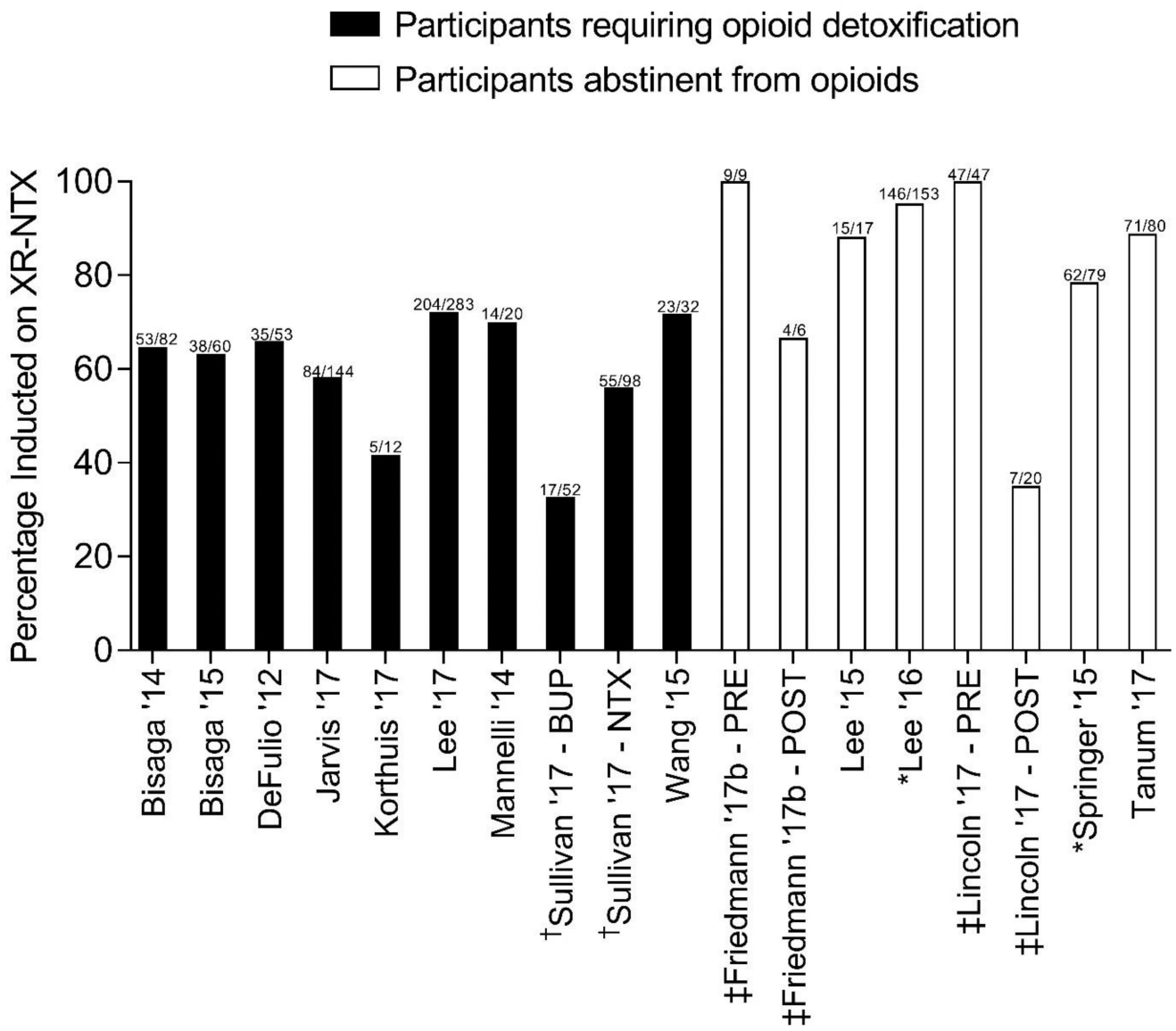
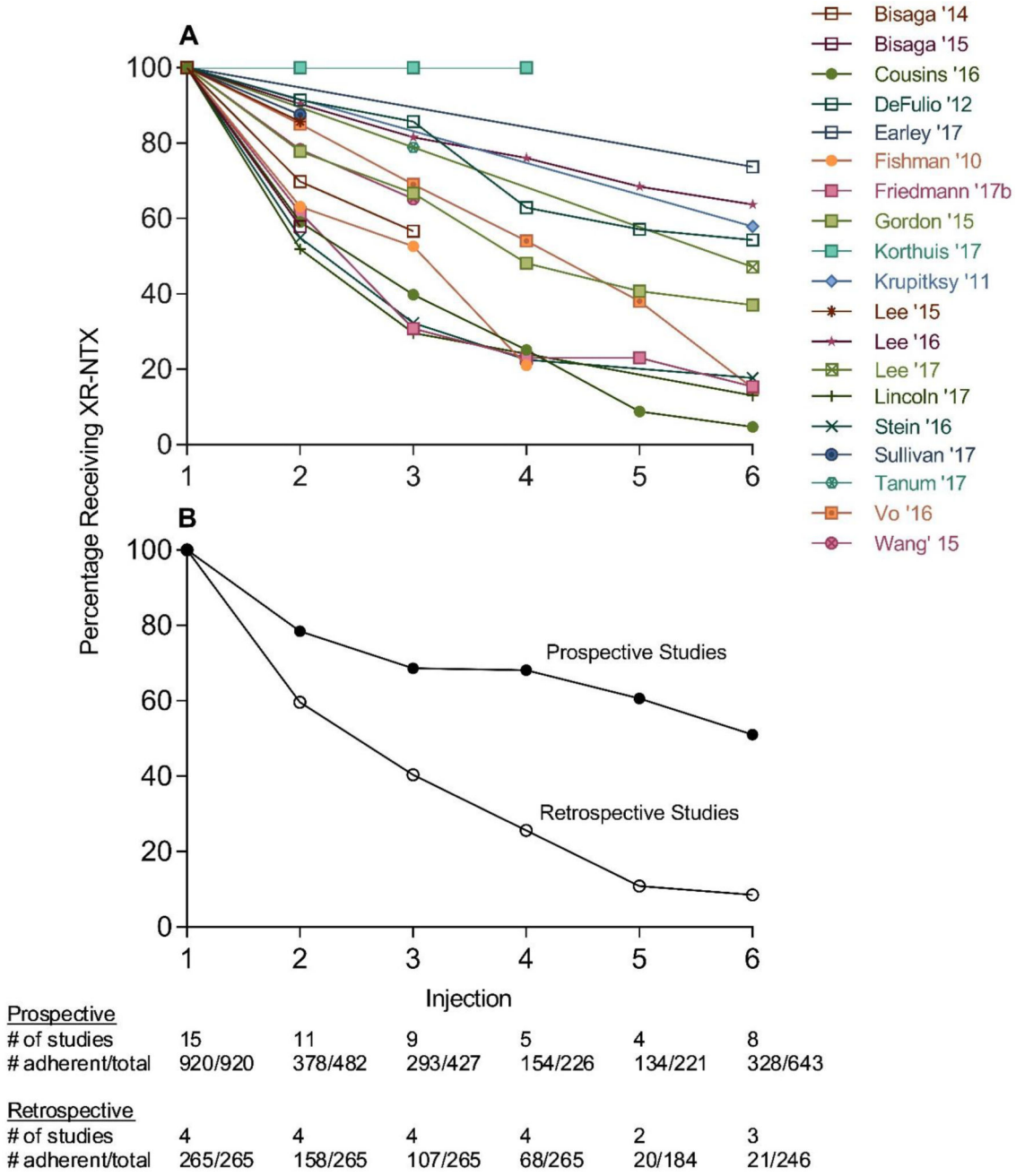


Figure 2.

Average rates of XR-NTX induction for 15 prospective studies. Numbers above each bar refer to the number of participants for each study (or group) who received their first injection of XR-NTX and the number of participants who were enrolled to receive XR-NTX. * = these studies did not exclude individuals who were actively using opioids but over 90% of participants in these studies did not require opioid detoxification. † = Induction rates significantly different between groups. See “Factors associated with induction” section for more detailed description of detox procedures. ‡ = Statistical comparisons not reported for induction outcomes. PRE and POST refer to whether induction occurred in jail before release (PRE) or in the community after release (POST).



Prospective						
# of studies	15	11	9	5	4	8
# adherent/total	920/920	378/482	293/427	154/226	134/221	328/643
Retrospective						
# of studies	4	4	4	4	2	3
# adherent/total	265/265	158/265	107/265	68/265	20/184	21/246

Figure 3.

(A) Average rates of adherence at each injection from prospective (n = 15) and retrospective studies (n = 4). Data from three studies (58, 59, 63) are not shown because outcomes were not reported as percentage receiving each injection. (B) Average rates of adherence from prospective (closed circles) and retrospective studies (open circles). *Note*: Adherence rates shown are only for individuals who received their first XR-NTX injection. Including induction failures when calculating adherence decreases rates substantially (see "Adherence to XR-NTX" in Discussion).

Table 1

General characteristics of included studies and their reported outcomes

Author (reference)	Year	OUD population	Design	Duration (mos.)	XR-NTX comparator	Other comparator	Outcomes
Prospective studies							
Bisaga (44)	2014	Adults	Randomized, double-blind (to adjunctive medications), placebo-controlled, parallel-group	3	None, all offered open-label XR-NTX	Memantine vs. placebo	Induction, adherence, opioid use
Bisaga (45)	2015	Adults with histories of marijuana use	Randomized, double-blind (to adjunctive medications), placebo-controlled, parallel-group	2	None, all offered open-label XR-NTX	Dronabinol vs. placebo	Induction, adherence, opioid use
DeFulio (46)	2012	Unemployed heroin-dependent adults	Randomized, open-label, parallel-group	6	None, all offered XR-NTX	Employment-based reinforcement for XR-NTX adherence (Incentives) vs. noncontingent reinforcement (Control)	Induction, adherence, opioid use
Earley (57)	2017	Healthcare professionals	Uncontrolled, open-label	24	None, all offered XR-NTX	None	Adherence, opioid use, overdose
Friedmann (42)	2017b	Adult inmates	Randomized, open-label, controlled, parallel-group, pilot	6	None, all offered XR-NTX	XR-NTX initiation pre- versus post-release	Induction, adherence, opioid use, overdose
Gordon (55)	2015	Pre-release adult inmates	Uncontrolled, open-label pilot	7	None, all offered XR-NTX	Participants who accepted all XR-NTX injections (Completers) vs. those not accepting all (Non-completers)	Adherence, opioid use, overdose
Jarvis (51)	2017	Unemployed heroin-dependent adults	Uncontrolled pre-randomization phase of ongoing study	1–4 (wks.)	None	None	Induction
Korthuis (49)	2017	HIV-positive adults	Randomized, open-label, controlled, parallel-group, pilot	4	Treatment as usual	Participants with OUD (with or without AUD) vs. AUD-only[a]	Induction, adherence, opioid use, overdose
Krupitksy (27)	2011	Russian adults	Randomized, double-blind, placebo-controlled, parallel-group	6	Placebo	None	Adherence, opioid use, overdose
Krupitsky (56)	2013	Participants who completed Krupitsky et al. (2011)	Uncontrolled, open-label extension of Krupitsky et al. (2011)	12	None, all offered XR-NTX	Participants continuing XR-NTX (XR-NTX->XR-NTX) vs. participants switching from placebo to XR-NTX (PBO->XR-NTX)	Adherence, opioid use, overdose

Author (reference)	Year	OUD population	Design	Duration (mos.)	XR-NTX comparator	Other comparator	Outcomes
Lee (41)	2015	Pre-release adult inmates	Randomized, open-label, controlled, parallel-group, pilot	2	Treatment referral	None	Induction, adherence, opioid use, overdose
Lee (28)	2016	Adult criminal justice offenders with histories of opioid dependence	Randomized, open-label, controlled, parallel-group	6	Treatment referral	None	Induction, adherence, opioid use, overdose
Lee (36)	2017	Adults	Randomized, open-label, controlled, parallel-group	6	Buprenorphine	None	Induction, adherence, opioid use, overdose
Lincoln (38)	2017	Adult inmates	Prospective cohort study	6	None, all offered XR-NTX	XR-NTX initiation pre- versus post-release	Induction, adherence, overdose
Mannelli (47)	2014	Adults	Uncontrolled, open-label pilot	1	None, all offered XR-NTX	None	Induction, opioid use
Springer (43)	2015	HIV-positive pre-release adult inmates	Randomized, double-blind, placebo-controlled, parallel-group	1[b]	Placebo	Participants with AUD vs. OUD[a]	Induction
Sullivan (50)	2017	Adults	Randomized, open-label, controlled, parallel-group	1 (5 wks.)	None, all offered XR-NTX	Naltrexone- vs. buprenorphine-assisted detox	Induction, adherence, opioid use, overdose
Tanum (37)	2017	Norwegian adults	Randomized, open-label, controlled, parallel-group	3	Buprenorphine	None	Induction, adherence, opioid use, overdose
Wang (48)	2015	Injecting, heroin-dependent adults	Open-label, crossover (pre- and post-XR-NTX)	3	None, all offered XR-NTX	None	Induction, adherence, opioid use
Retrospective studies							
Baser (58)	2011	Commercially insured adults	Pre- vs. post-XR-NTX treatment	6[c]	Oral NTX, buprenorphine, and methadone	Patients treated with any medication vs. no medication[a]	Adherence
Cousins (61)	2016	Adults enrolled in county-funded treatment	Post-XR-NTX over time	Variable[d]	None, all received XR-NTX	Heroin vs. non-heroin users	Adherence, overdose
Crits-Cristoph (39)	2015	Adults under community supervision	Pre- and post-outpatient XR-NTX treatment	Variable[d]	Oral NTX, buprenorphine, and no medication	Patients with OUD vs. AUD[a]	Opioid use
Crits-Cristoph (40)	2016	Adults	Pre- and post-outpatient XR-NTX treatment	Variable[d]	Oral NTX, buprenorphine, and no medication	Patients with OUD vs. AUD[a]	Opioid use
Fishman (22)	2010	Adolescents and young adults	Post-XR-NTX over time	4[e]	None, all received XR-NTX	None	Adherence, opioid use, overdose
Herbeck (64)	2016	Adults enrolled in county-funded treatment[f]	Post-XR-NTX over time	Variable[d]	None	Patients with OUD vs. AUD[a], men vs. women	Adherence

Author (reference)	Year	OUD population	Design	Duration (mos.)	XR-NTX comparator	Other comparator	Outcomes
Leslie (53)	2015	Privately insured adults attending residential rehabilitation	Post- XR-NTX over time	1[g]	Recommended for but did not receive XR-NTX	None	Induction
Sajid (59)	2016	Dually-diagnosed adults	Pre- and post-XR-NTX	Variable[d]	None, all received XR-NTX	Patients with OUD only vs. AUD only[a] vs. OUD + AUD	Adherence, opioid use
Stein (60)	2016	Adults	Post-XR-NTX over time	Variable[d]	None, all received XR-NTX	None	Adherence
Vo (62)	2016	Adolescents and young adults	Post-XR-NTX over time	6	Buprenorphine	None	Adherence, opioid use
Williams (63)	2017	Subsample of participants from Sullivan et al. (2017)	Follow-up cross-sectional survey after completing parent study	Variable[h]	None, all offered XR-NTX	Participants with complete vs. intermittent vs. no XR-NTX adherence	Adherence, opioid use, overdose
Secondary analyses							
Friedmann (66)	2017a	Same participants as Lee et al. (2016)	Moderator analysis of XR-NTX	6	Treatment as usual	None	Opioid use
Mogali (54)	2015	Adults	Predictors of induction success in three clinical studies[i]	7 (days)[i]	None	None	Induction
Nunes (65)	2015	Same participants as Krupitsky et al. (2011)	Moderator analysis of XR-NTX	6	Placebo	None	Opioid use
Nunes (67)	2017	Same participants as Lee et al. (2016)	Moderator analysis of XR-NTX	6	Treatment as usual	None	Opioid use

[a] Outcomes not reported in this review.

[b] Study is ongoing. The manuscript reports outcomes through 2 injections (i.e, 2 months), but adherence to 2nd injection is not reported in this review because investigators were blind to whether injections were XR-NTX or placebo, which could impact adherence (27).

[c] Refers to post-XR-NTX duration.

[d] Naturalistic study. Duration based on length individuals decided to remain in treatment.

[e] Some patients remained in treatment longer than 4 months. 4 months used as outcome because data were reported at this time point for all participants.

[f] Sample overlaps with that used in (61). Only outcomes not reported in that study are reported for (64).

[g] Variable but included patient's residential stay (< 1 month) through follow-up, which occurred ≤10 days post-discharge

[h] Average time since study completion was 21 months

[i] One of the three studies was (45). Data were obtained from 150 consecutive admissions, and the total number of participants used from this study is not reported.

[j] Study only included data on inpatient induction, which used a 7-day protocol.

Table 2

Quality assessments

Author (reference)	Year		Cochrane Collaboration's Tool						
		Outcome	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other bias
Randomized controlled trials									
Bisaga (44)	2014	Induction	Low	Low	Low	Unclear[e]	Low	Low	Unclear[c]
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Unclear[c]
		Opioid use	Low	Low	High[a]	Unclear[e]	Unclear[b]	Low	Unclear[c]
Bisaga (45)	2015	Induction	Low	Unclear[e]	Low	Unclear[e]	Low	Low	Unclear[c]
		Adherence	Low	Unclear[e]	High[a]	Unclear[e]	Low	Low	Unclear[c]
		Opioid use	Low	Unclear[e]	High[a]	Unclear[e]	Unclear[b]	Low	Unclear[c]
DeFulio (46)	2012	Induction	Low	Low	Low	Unclear[e]	Low	Low	Low
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Low	Low	Low
Friedmann (42)	2017b	Induction	Low	Unclear[e]	Low	Unclear[e]	Low	Low	Low
		Adherence	Low	Unclear[e]	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Unclear[e]	High[a]	Unclear[e]	Unclear[b]	Low	Low
Korthuis (49) *	2017	Induction	Low	Low	Low	Unclear[e]	Low	Low	Low
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Low	Low	Low
Krupitsky (27)*	2011	Adherence	Low	Low	Low	Low	Low	Low	Low
		Opioid use	Low	Low	Low	Low	Unclear[b]	Low	Low
Lee (41) *	2015	Induction	Low	Low	Low	Unclear[e]	Low	Low	Low
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Low	Low	Low

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Author (reference)	Year								
			Cochrane Collaboration's Tool						
		Outcome	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other bias
Lee (28) *	2016	Induction	Low	Low	Low	Unclear[e]	Low	Low	Low
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Low	Low	Low
Lee (36) *	2017	Induction	Low	Low	High[a]	Low	Low	Low	Low
		Adherence	Low	Low	High[a]	Low	Low	Low	Unclear[f]
		Opioid use	Low	Low	High[a]	Low	Low	Low	Low
Springer (43)	2015	Induction	Low	Low	Low	Unclear[e]	Low	Low	Low
Sullivan (50)	2017	Induction	Low	Low	High	Unclear[e]	Low	Low	Unclear[d]
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Unclear[b]	Low	Low
Tanum (37) *	2017	Induction	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Adherence	Low	Low	High[a]	Unclear[e]	Low	Low	Low
		Opioid use	Low	Low	High[a]	Unclear[e]	Unclear[g]	Low	Low
			Downs and Black Checklist						
			Reporting quality (0– 11)	External validity (0– 3)	Bias (0–7)	Confounding (0–6)	Power (0,1)	Overall (0–28)	
Non-randomized studies									
Cousins (61)	2016	Adherence	11	1	5	4	0	21	
Earley (57)	2017	Adherence	11	0	5	4	0	20	
		Opioid use	11	0	5	2	0	18	
Fishman (22)	2010	Adherence	11	0	5	4	0	20	
		Opioid use	11	0	5	4	0	20	
Gordon (55)		Adherence	9	0	5	3	0	17	
		Opioid use	9	0	4	2	0	15	

Author (reference)	Year								
			Cochrane Collaboration's Tool						
		Outcome	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other bias
Herbeck (64)	2016	Adherence	9	1	5	3	0	18	
Jarvis (51)	2017	Induction	11	0	5	5	0	21	
Krupitsky (56)	2013	Adherence	10	0	5	4	0	19	
		Opioid use	11	0	5	3	0	18	
Mannelli (47)	2014	Induction	9	1	5	4	0	19	
		Opioid use	8	1	5	2	0	16	
Sajid (59)	2016	Adherence	8	1	3	4	0	16	
		Opioid use	8	1	3	2	0	14	
Vo (62)	2016	Adherence	10	0	4	3	0	17	
		Opioid use	9	0	4	3	0	16	
Wang (48)	2015	Induction	9	0	5	3	0	17	
		Adherence	8	0	5	3	0	16	
		Opioid use	9	0	4	1	0	14	
Williams (63)	2017	Adherence	9	0	4	2	0	15	
		Opioid use	9	0	4	2	0	15	
			Newcastle-Ottawa Scale						
			Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Overall (0–9)			
Cohort studies									
Baser (58)	2011	Adherence	4	2	3	9			
Crits-Cristoph (39)	2015	Opioid use	3	2	1	6			
Crits-Cristoph (40)	2016	Opioid use	3	2	1	6			
Leslie (53)	2015	Induction	4	2	3	9			
Lincoln (38)	2017	Induction	3	0	3	6			
	2017	Adherence	3	0	3	6			
Stein (60)		Adherence	4	2	3	9			

[a] XR-NTX not blinded.

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[b] Method of handling missing data not clear or possibly affected by differential retention between groups.

[c] Baseline differences between groups notcontrolled for.

[d] Role of standing adjuvant medications confounded with induction assignment.

[e] Not mentioned.

[f] Comparisons between adherence to XR-NTX and buprenorphine in different units (mean vs. median).

[g] It is stated that analyses were intent-to-treat, however, the CONSORT figure suggests analyses were per-protocol

[*] Denotes trials that experimentally isolated the effects of XR-NTX on opioid use.

Table 3

XR-NTX induction characteristics and success rates

Author (reference)	Year	Induction setting	Opioid abstinence required at outset	Detox procedures	Percent (number) inducted
Prospective studies					
Bisaga (44)	2014	Inpatient	No	7-day rapid detox	64.6% (53/82)
Bisaga (45)	2015	Inpatient	No	8-day rapid detox	63.3% (38/60)
DeFulio (46)	2012	Outpatient	No	1- to 4-wk incentive-based intervention for opioid abstinence and oral NTX adherence	66.0% (35/53)
Friedmann (42)	2017b	Jail & outpatient after release	Yes	Pre-release vs. post-release	Pre-release: 100% (9/9); post-release: 66.7% (4/6)
Jarvis (51)	2017	Outpatient	No	1- to 4-wk incentive-based intervention for opioid abstinence and oral NTX adherence	58.3% (84/144)
Korthuis (49)	2017	Outpatient	No	Not reported	41.7% (5/12)
Lee (41)	2015	Jail	Yes	None	88.2% (15/17)
Lee (28)	2016	Inpatient and outpatient[a]	Yes	Not reported	95.4% (146/153)
Lee (36)	2017	Inpatient	No	Varied by site[b]	72.1% (204/283)
Lincoln (38)	2017	Jail & outpatient after release	Yes	Pre-release vs. post-release	Pre-release: 100% (47/47); post-release: 35% (7/20)
Mannelli (47)	2014	Outpatient	No	8-day rapid detox	70.0% (14/20)
Springer (43)	2015	Outpatient, within 1 wk of release from prison/jail	No, but nearly all were abstinent	None	78.5% (62/79)
Sullivan (50)	2017	Outpatient	No	7-day rapid detox with oral NTX vs. 7-day buprenorphine detox with 7-day washout	NTX-assisted detox: 56.1% (55/98); buprenorphine-assisted detox: 32.7% (17/52)[c]
Tanum (37)	2017	Outpatient	Yes	Not reported	88.9% (71/80)
Wang (48)	2015	Outpatient	No	Not reported	71.9% (23/32)
Retrospective studies					
Leslie (53)	2016	Residential rehabilitation	Not reported	Not reported	28.1% (168/598)[d]

[a] Details regarding induction setting reported in (67)

[b] Details regarding induction setting reported in (75)

[c] NTX-assisted detox XR-NTX induction rate significantly higher than buprenorphine-assisted detox

[d] Numbers reported for patients who were recommended for XR-NTX

Table 4

Rates of XR-NTX adherence

Author (reference)	Year	Maximum number of injections	Mean (SD) number injections received all[a]	Mean (SD) number injections received initiators[b]
Prospective studies				
Bisaga (44)[c]	2014	3	1.5 (1.3)	2.3 (0.9)
Bisaga (45)	2015	2	1.0 (0.9)	1.6 (0.5)
DeFulio (46)[d]	2012	6	3.0 (2.6)	4.5 (1.8)
Earley (57)[f]	2017	24	Not applicable[e]	Not reported
Friedmann (42)[d]	2017b	6	2.2 (2.0)	2.5 (1.9)
Gordon (55)	2015	7	Not applicable[e]	4.1 (2.5)
Korthuis (49)	2017	4	1.7 (2.1)	4.0 (0.0)
Krupitsky (27)[f]	2011	6	Not applicable[e]	Not reported
Krupitsky (56)[f,g]	2013	13	Not applicable[e]	Not reported
Lee (41)	2015	2	1.6 (0.7)	1.9 (0.4)
Lee (28)	2016	6	4.6 (2.0)	4.8 (1.8)
Lee (36)	2017	6	Not applicable[e]	3.9[j]
Lincoln (38)[d]	2017	3[h]	1.5 (1.1)	1.8 (0.9)
Sullivan (50)[d]	2017	2	0.9 (1.0)	1.9 (0.3)
Tanum (37)	2017	3	Not reported	Not reported
Wang (48)	2015	3	1.8 (1.3)	2.4 (0.8)
Retrospective studies				
Baser (58)	2011	6[i]	Not applicable[e]	2.0[j]
Cousins (61)	2016	7+[k]	Not applicable[e]	2.4 (1.5)
Fishman (22)	2010	4[l]	2.4 (1.3)	2.7 (1.3)
Sajid (59)	2016	Not reported[m]	Not applicable[e]	2.7 (2.6)
Stein (60)	2016	6+[k]	Not applicable[e]	2.5 (1.9)
Vo (62)	2016	6	Not applicable[e]	3.6 (1.8)[n]
Williams (63)[o]	2017	Variable[p]	Not applicable[e]	6.1 (1–14)[q]

[a] Refers to all participants who intended to receive XR-NTX. Individuals who did not receive their first injection were included.

[b] Refers only to participants who initiated XR-NTX. Those who did not initiate XR-NTX were excluded.

[c] Treatment retention differed significantly by experimental group. Adherence rates were not explicitly tested but were similar. See Supplemental Figure 1.

[d] Adherence rates differed significantly by experimental group based on all participants or initiators only. See Supplemental Figure 1.

[e] All participants included in the analyses of adherence received their first injection.

[f] Data on adherence were limited to the percentage of participants receiving all injections or injections at specific time points rather than continuously. These data are shown graphically in Figure 3 Panel A.

[g] 12-month open-label continuation trial including participants from (27) who received XR-NTX or placebo.

[h] 6 injections were offered but adherence for the 4th and 5th injections was not reported and therefore means and SDs could not be calculated for all 6 injections. Outcomes reported here are for the first 3 injections.

[i] The observation window was 6 months.

[j] Standard deviation not reported.

[k] Categories without an upper bound were counted as their lower bound in computing means and standard deviations (e.g., 7+ treated as 7).

[l] Observation period available for entire sample was 4 months. One participant received 5 injections during this period.

[m] Average observation period after XR-NTX initiation was approximately 7 months.

[n] Number differs from original manuscript (4.1 injections), which excluded participants who only received one injection from the mean calculation.

[o] Subsample of participants (34%) from (50) who completed a follow-up survey after the parent trial.

[p] Average follow-up time since study completion was 21 months.

[q] SD could not be calculated. Range, which was reported, is shown instead. These numbers refer only to the subsample of participants who completed the follow-up survey and received XR-NTX after the parent trial ended.

Table 5

Study characteristics and opioid use outcomes

Author (reference)	Year	Opioid use outcome measure(s)	Method(s) of handling missing outcomes	Findings
Prospective studies that *did* experimentally isolate the effects of XR-NTX on opioid use (i.e., RCTs of XR-NTX)				
Korthuis (49)	2017	Change (baseline to 4 mos.) in past 30-day opioid use, % change in opioid-positive urine	Missing-missing only (<2% missing, however)	Statistical comparisons were not performed. Decrease from baseline to 4 mos. (XR-NTX: 20.3 to 7.7 days; TAU: 17.3 to 4.1 days). Change in % opioid-positive from baseline to 4 mos. (XR-NTX: 75% to 40%; TAU: 75% to 58.3%).
Krupitsky (27)	2011	% of wks of confirmed opioid abstinence, % of participants with continuous confirmed abstinence, % opioid-free days, % of participants with a positive naloxone test, % achieving at least 90% of wks abstinent from opioids	Misssing-positive only	Compared to placebo, XR-NTX group had higher % wks of confirmed abstinence (90.0% vs. 35.0%), higher % of participants with continuous confirmed abstinence (35.7% vs. 22.6%), higher % of opioid-free days (99.2% vs. 60.4%), higher % with 90% wks abstinent (51.6% vs. 31.5%) and lower % of participants with positive naloxone test (0.8% vs. 13.7%)
Lee (41)	2015	Opioid relapse[c] by wks 4 and 8, confirmed opioid abstinence through wks 4 and 8, % of urine samples negative for opioids through wks 4 and 8	Missing-positive and last observed inputation	Compared to treatment referral, the XR-NTX group had lower rates of opioid relapse at wks 4 (37.5% vs. 88.2%) and 8 (50.0% vs. 94.1%), higher confirmed abstinence through wks 4 (50.0% vs. 11.8%) and 8 (50.0% vs. 5.9%), and higher rates of opioid-negative urine samples through wks 4 (58.5% vs. 28.9%) and 8 (59.6% vs. 24.2%).
Lee (28)	2016	Time to opioid relapse[c], % who relapsed to opioids, % of opioid-negative urines, % of 2-wk intervals with confirmed opioid abstinence, % days opioid use	Missing-positive and alternative analysis	Compared to treatment referral, XR-NTX group had a longer time to relapse (10.5 vs. 5.0 wks), higher % of opioid-negative urines (74.1% vs 55.7%), higher % of intervals of confirmed abstinence (71.1% vs. 49.5%), lower % days opioid use (4.6% vs. 12.7%), and lower % relapse (43.1% vs. 63.9%). There were no differences between XR-NTX and treatment referral on % of opioid-negative urines at the 52- (49% vs. 46%) and 78-wk follow-ups (46% vs. 46%)
Lee (36)	2017	Time to opioid relapse[h], % who relapsed to opioids, weekly opioid-negative urine samples	Missing-positive only	Compared to buprenorphine, XR-NTX group had a shorter time to relapse (8.4 vs. 14.4

Author (reference)	Year	Opioid use outcome measure(s)	Method(s) of handling missing outcomes	Findings
		(of 24), self-reported opioid-free days (of 144)		wks), higher % relapse (65% vs. 57%), fewer opioid-negative urine samples (4 vs. 10), and fewer self-reported opioid-free days (39 vs. 81).[i]
Tanum (37)	2017	% of urine samples negative for illicit opioids, days of heroin use, days of other illicit opioid use	Missing-positive only	Compared to buprenorphine, XR-NTX group was noninferior[j] on urine samples negative for opioids (90% vs. 80%), and had lower heroin use (mean difference −3.2 days), and other illicit opioid use (mean difference −2.7 days).
Prospective studies that did *not* experimentally isolate the effects of XR-NTX on opioid use				
Bisaga (44)	2014	Weekly % who used opiates	Unclear	% who used opiates did not differ between the memantine and placebo groups. Actual % for each group not reported. 64% used opiates once or more 1 mo. after 1st injection. 43% used opiates 1 mo. after 2nd injection.
Bisaga (45)	2015	Weekly % who used opiates	Unclear	% who used opiates did not differ between the dronabinol and placebo groups. Actual % for each group not reported. 63% used opioids at least once during trial.
DeFulio (46)	2012	% of urine samples negative for opiates	Missing-positive and missing-missing.	There was no difference on opiate abstinence between the Incentives (71.6%) and Control group (65.3%)[a].
Earley (57)	2017	% of participants who tested positive for opioids, % of participants who relapsed to opioids[b]	Missing-missing only	10.5% tested positive for opioids. 75% of these participants tested positive once only. No retained participants relapsed to opioids.
Friedmann (42)	2017b	% of days confirmed opioid abstinence through wk 4, days confirmed abstinent through wk 4, % urine samples positive for opioids through 6 mos., time to opioid relapse[c], % of participants who relapsed to opioids	Missing-positive only	Pre-release group had higher % of days (83% vs. 46%) and number of days confirmed abstinence (Means = 23 vs. 13; Medians = 28 vs. 11) than post-release through wk 4[d]. Pre-release group had lower % of opioid-positive urine samples through 6 mos than post-relase (22% vs. 33%).Time to relapse was longer in the pre-release group compared to post-release (9 vs. 5 [medians] and fewer relapsed to opioids (77.8% vs. 100%).
Gordon (55)	2015	% of participants who used opioids through follow-up	Missing-missing only	Fewer completers (20.0%) used opioids than non-completers (68.8%)[e]

Author (reference)	Year	Opioid use outcome measure(s)	Method(s) of handling missing outcomes	Findings
Krupitsky (56)	2013	% of participants with continuous confirmed abstinence, % urine samples negative for opioids, % opioid-free days, past 30-day opioid use	Missing-positive only	There were no differences between the XR-NTX->XR-NTX and PBO-> XR-NTX groups on % of participants with continuous confirmed abstinence (49.3% vs. 53.2%), % of urine samples negative for opioids (73.7% vs. 81.0%), % opioid-free days (80.6% vs. 87.4%), and past 30-day opioid use (both groups < 1 day).
Mannelli (47)	2014	% opioid-positive urines	Unclear	21.2% of urines were positive for opioids
Sullivan (50)	2017	% abstinent for 2 consecutive wks (at 4- and 5-wks post-XR-NTX)	Unclear	80.6% were abstinent during this 2-wk period. Abstinence did not differ based on detox type (NTX vs. buprenorphine; 78.2% vs. 88.2%)
Wang (48)	2015	% opioid-positive urines	Missing-missing only	Compared to pre-XR-NTX (100%) % opioid-positive urines were lower at wks 4 (5.8%), 8 (5.6%), 12 (18.9%), and 14 (54.1%).[k]
Retrospective studies				
Crits-Cristoph (39)	2015	Change in opioid abstinence from baseline to treatment completion	Not applicable[l]	Patients receiving XR-NTX had greater increases in abstinence (54.5%) than those receiving buprenorphine (6.8%) and no medication (8.2%) but not oral NTX (17.9%).
Crits-Cristoph (40)	2016	Change in opioid abstinence from baseline to treatment completion	Not applicable[l]	Patients receiving XR-NTX had no greater change in abstinence (39.6%) than those receiving oral NTX (27.2), buprenorphine (45.6%), or no medication (38.9%)
Fishman (22)	2010	Substantial reduction in opioid use[m]	Missing-positive only	68.8% had substantial reductions in use
Sajid (59)	2016	% change in opioid-positive urines before and after starting XR-NTX	Not applicable[l]	There was a significant decrease in opioid-positive urines pre- (32.2%) and post-XR-NTX (24.0%)[n].
Vo (62)	2016	% opioid-negative urines	Missing-positive and missing-missing reported and analyzed	There were no differences in % opioid-negative urines between XR-NTX and buprenorphine groups (50% at 12 wks, 39% at 24 wks[o]).
Williams (63)	2017	% of participants who used opioids ≥ once since study completion[p], % of participants who used opioids in past mo., % of participants who progressed to daily opioid use, time to daily opioid use	Missing-missing[q]	77.2% used an opioid after parent study and 31.6% used opioid in past mo (neither differed across groups). Participants with complete XR-NTX adherence in parent study were less likely to progress to daily use (40.7%) than intermittent (63.6%) and non-adherent (84.2%) participants and took longer to

Author (reference)	Year	Opioid use outcome measure(s)	Method(s) of handling missing outcomes	Findings
				do so (68.3 vs. 12.4 vs. 5.5 days).

[a]Data are reported as missing-positive from monthly samples. Comparisons counting missing data as missing and collected at weekly intervals also did not differ between groups.

[b]Defined as positive naloxone challengetest.

[c]Defined as 10 self-reported days of opioid use in a 4-week period and/or two consecutive positive or missing urines.

[d]Group results are descriptive only. Sample sizes were small (ns <10) and not powered to detect statistically significant differences.

[e]Outcomeswere reported through 9 months (XR-NTX was available for first 7 months). Data are reported as combination of self-report and urine testing. Comparison was also significant using urine testing only.

[f]Outcome was reported in a separate secondary analysis (65).

[g]Requring two consecutive confirmed measures of opioid use to define the primary outcome (relapse).

[h]Defined as any week (after a 20-day grace period) during which the participant reported at least 1 day of non-study opioid use, provided a urine sample that was positive for non-study opioids, or did not provide a urine sample.

[i]Results are from the primary analysis (intent-to-treat). A per protocol analysis among individuals who received study medication (excluding induction failures) found no difference between buprenorphine and XR-NTX.

[j]Noninferiority margin was set at 20%.

[k]Percentages were only reported graphically and were extracted using WebPlotDigitizer (76).

[l]Record/chart reviewsof routine care. Missed visits/data were not mentioned.

[m]Defined as continous abstinence or discrete lapses ≤ once per week verified by self-report and urinalysis.

[n]Analysis combined patientswith OUD and OUD + AUD. Percentages are for OUD-only group.

[o]Percentages were reported graphically by week. Unable to extract overall percentage because group ns at each week not reported.

[p]Average time since study completion was 21 months.

[q]Opioid outcomes were based on self-report but some participants provided urine samples, which were consistent with self-report.