



# Meeting the Need

Doing more to help address the crisis of opioid and alcohol dependence

## ISSUE 4:

# Research Update: Medication-Assisted Treatment of Opioid Dependence

A LOOK AT 2 PUBLICATIONS COMPARING TREATMENT OPTIONS,  
WITH STEERING COMMITTEE COMMENTARY

The year 2017 marked a milestone for research on the treatment of opioid dependence. For the first time, clinical trial data became available regarding the comparative effectiveness of buprenorphine-naloxone and extended-release naltrexone. This newsletter reviews an open-label study (known as X:BOT) published by Lee and colleagues in *The Lancet* and an open-label study published by Tanum and colleagues in *JAMA Psychiatry*.<sup>1,2</sup> This overview also includes commentary from members of the **Meeting the Need** Steering Committee.

The X:BOT study evaluated patients with opioid use disorder based on *Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5)*, criteria.<sup>1</sup> VIVITROL® (naltrexone for extended-release injectable suspension) was approved based on *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR)*, criteria for opioid dependence.

## IMPORTANT SAFETY INFORMATION

### INDICATIONS

#### VIVITROL is indicated for:

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
- Prevention of relapse to opioid dependence, following opioid detoxification.
- VIVITROL should be part of a comprehensive management program that includes psychosocial support.

### CONTRAINDICATIONS

#### VIVITROL is contraindicated in patients:

- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- Who have exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

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Please see [Prescribing Information and Medication Guide](#).  
Review the [Medication Guide](#) with your patients.

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\*The Steering Committee members reviewed the article summaries but did not author them. All members are paid consultants of Alkermes, Inc. Visit [MeetingTheNeed.CurrentPsychiatry.com](#) for a list of faculty disclosures.

## Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial.<sup>1</sup>

Lee JD et al. *Lancet*. January 2018. (X:BOT)

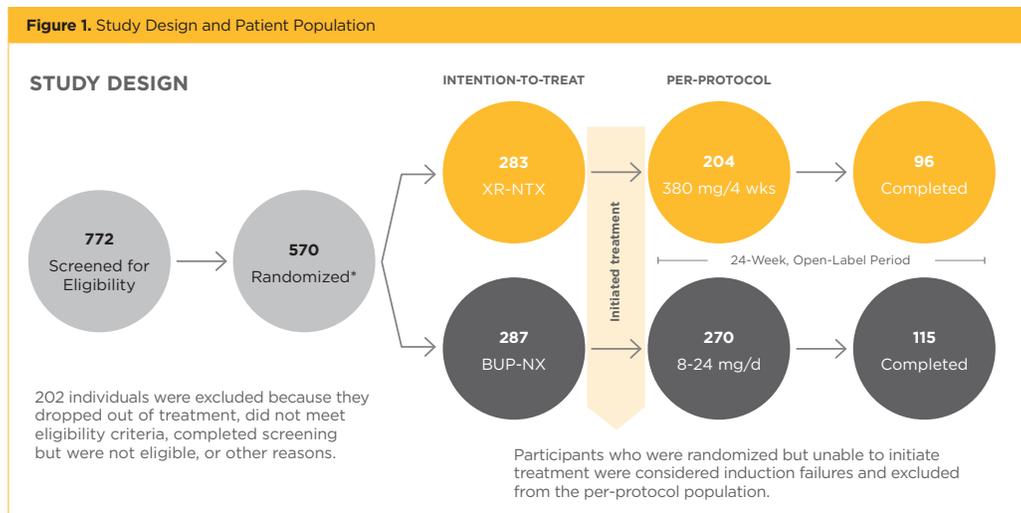
### Design

This US study, called X:BOT, was a 24-week, multicenter, open-label, randomized clinical trial of adult (age ≥18 years) outpatients with opioid use disorder (DSM-5 criteria). It was designed to compare the effectiveness of extended-release naltrexone (XR-NTX) versus sublingual buprenorphine-naloxone (BUP-NX) for the prevention of relapse.

The National Institute on Drug Abuse (NIDA) Clinical Trials Network sponsored the study. The authors and the study sponsor designed and implemented the study, collected and analyzed the data, wrote the initial manuscript draft, and were responsible for data integrity. Indivior PLC donated BUP-NX and had access to periodic safety data only, with no input on or review of this manuscript. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

A total of 772 participants were recruited and screened during voluntary, usual-care, inpatient detoxification admissions. All eligible subjects had used non-prescribed opioids in the previous 30 days. A total of 570 participants were randomized to receive either daily sublingual self-administered BUP-NX 8 mg/day to 24 mg/day (n=287) or XR-NTX 380 mg administered intramuscularly every fourth week (n=283) (Figure 1).

Figure 1. Study Design and Patient Population



\*217 randomized early; 353 randomized late.  
BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

### Commentary from the Steering Committee

#### Q: What is the main takeaway from these publications?

**Dr. Paolo Mannelli:** These studies are important because they were the first to compare the effectiveness of extended-release naltrexone and buprenorphine-naloxone. The findings of the studies showed that they can be equally effective once patients are on treatment.

**Dr. Laura Bamford:** These studies indicated that the agents were similar with respect to efficacy after treatment was started. The data support providers and patients having more treatment choices, based on the needs of individual patients.

**Dr. Jeffrey Berman:** Both studies have shown that, after successful induction, extended-release naltrexone and buprenorphine-naloxone proved comparable in preventing relapse. But it's important to remember that getting people through that minimum 7- to 10-day opioid-free duration that's recommended before initiating VIVITROL is to avoid precipitation of opioid withdrawal severe enough to require hospitalization.

**Dr. Laura Leahy:** These studies demonstrated that extended-release naltrexone and buprenorphine-naloxone have comparable safety and efficacy once you get patients through detoxification.

**Dr. Genie Bailey:** It's important to point out that both of these study designs had limitations. Overall, these studies showed that extended-release naltrexone and buprenorphine-naloxone looked comparable for patients who can get through detoxification prior to initiating treatment with extended-release naltrexone. Also, providers now have more data to help make a complex treatment decision.

(Continued on page 3)

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

#### Vulnerability to Opioid Overdose:

- After opioid detoxification, patients are likely to have a reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. As the blockade wanes and eventually dissipates completely, use of previously tolerated doses of opioids could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).
- Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.

Please see Important Safety Information for VIVITROL throughout this newsletter.  
Please see Prescribing Information and Medication Guide.  
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Participants assigned to early randomization were randomized within 72 hours of last opioid use, including opioids used for detoxification. Participants randomized more than 72 hours after last opioid use were included in the late-randomization group.

XR-NTX treatment could be initiated at least 3 days from the patient's last opioid use, an opioid-negative urine drug test (UDT), and a negative naloxone challenge. These criteria were not met by 79 participants. BUP-NX treatment could be initiated once withdrawal symptoms emerged. This criterion was not met by 17 participants.

Additional exclusion criteria included the presence of serious medical, psychiatric, or substance use disorders; liver function tests greater than 5 times the upper limit of normal; suicidal or homicidal state; allergy or sensitivity to XR-NTX or BUP-NX; and inability to have safe intramuscular XR-NTX treatment. Women who were or could become pregnant or were breastfeeding were also excluded.

The intention-to-treat (ITT) population included all randomized participants. The per-protocol population included only the participants who began study medication.

**ENDPOINTS**

The primary endpoint was time to relapse. Relapse was defined as opioid use after Day 20—either 4 consecutive weeks with at least 1 day of non-study opioid as measured by a weekly UDT or 7 consecutive days with self-reported opioid use. Secondary endpoints reported in this publication included the proportion of participants initiated onto study medication, safety, frequency of non-study opioid use, and opioid craving. Other secondary outcomes evaluated in this study were not reported in the publication.

**Results**

Demographic data for the 570 randomized patients are shown in **Table 1**. The population was about 70% male and about 75% white and had about 12 years of opioid use on average.

For XR-NTX, treatment was initiated in 53% of participants (n=57) in the early randomization group and 84% of participants (n=148) in the late-randomization group.

<b>Table 1. Demographics and Baseline Clinical Characteristics</b>		
	<b>Intention to Treat (N=570)</b>	
	<b>Extended-release Naltrexone (n=283)</b>	<b>Buprenorphine-Naloxone (n=287)</b>
Age, years	34.0 (9.5)	33.7 (9.8)
Male	69%	72%
Female	31%	28%
White	73%	75%
Opioid use, years	12.8 (9.0)	12.2 (9.0)
Opioid used in the 7 days before detox admission		
Heroin	81%	81%
Opioid analgesic	15%	16%
Buprenorphine	2%	1%
Methadone	1%	1%

Data are mean (standard deviation).

*(Continued from page 2)*

**Commentary from the Steering Committee**

**Q: What else do these publications add to the conversation about extended-release naltrexone?**

**Dr. Jeffrey Berman:** One thing to note about the Tanum study was the non-inferiority of extended-release naltrexone with respect to days of use of heroin and other illicit opioids—and the lower number of days of illicit opioid use in the extended-release naltrexone group.

**Dr. Laura Leahy:** In the X:BOT study, subjective opioid craving declined rapidly from baseline in both treatment groups.

**Dr. Paolo Mannelli:** Keeping in mind the study limitations for both trials, the results suggest that opioid dependence can be effectively treated with a monthly, non-opioid medication.

**Dr. Thomas Kosten:** As seen in the Tanum study, once a patient gets on extended-release naltrexone, the treatment retention time can be comparable to that of buprenorphine-naloxone.

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (cont.)**

**Vulnerability to Opioid Overdose (cont.):**

- Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids.
- Any attempt by a patient to overcome the VIVITROL blockade by taking opioids may lead to fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

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**Relapse (primary endpoint) in the ITT population**

In the ITT population, opioid-relapse events occurred in 65% of XR-NTX-treated patients and in 57% of BUP-NX-treated patients (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.02 to 2.01;  $P=0.036$ ; **Figure 2**), mainly because many randomized participants in the ITT population did not initiate treatment with XR-NTX. Study sites varied in detoxification protocols and length of inpatient stay. Protocols included no opioids, 3- to 5-day methadone tapers, and 3- to 14-day buprenorphine tapers.

In this ITT population, the median time to relapse was 8.4 weeks in the XR-NTX group and 14.4 weeks in the BUP-NX group (hazard ratio [HR], 1.36; 95% CI, 1.10 to 1.68;  $P=0.004$ ).

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**Commentary from the Steering Committee**

**Q: What are some of the unanswered questions about these studies?**

**Dr. Jeffrey Berman:** One question is: What specific psychosocial interventions were provided? Psychosocial therapy is an important part of treatment.

**Dr. Laura Leahy:** One of the things that may not be clear to some readers of these articles is the fact that extended-release naltrexone is not an opioid. Healthcare providers should clearly communicate this when reviewing treatment options with patients and caregivers.

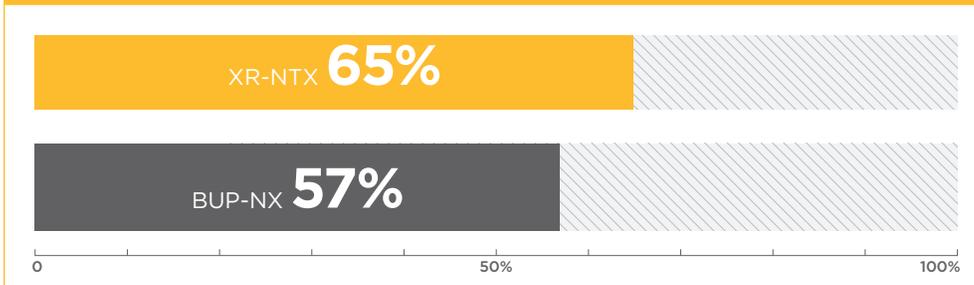
**Linda Frazier:** These studies indicated that extended-release naltrexone and buprenorphine-naloxone can both be effective medicines. However, how do providers identify who is right for which treatment?

**Dr. Genie Bailey:** Also what role does patient preference play in treatment outcomes?

**Dr. Paolo Mannelli:** I have questions about the detoxification protocols. There was not a lot of detail about the detoxification protocols used, and the protocols varied. [For more information on detoxification, refer to the VIVITROL question-and-answer page on the Meeting the Need website.]

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**Figure 2.** Opioid Relapse (Weeks 3-24) in the ITT Population



Odds ratio, 1.44; 95% confidence interval, 1.02 to 2.01;  $P=0.036$ . BUP-NX, buprenorphine-naloxone; ITT, intention-to-treat; XR-NTX, extended-release naltrexone.

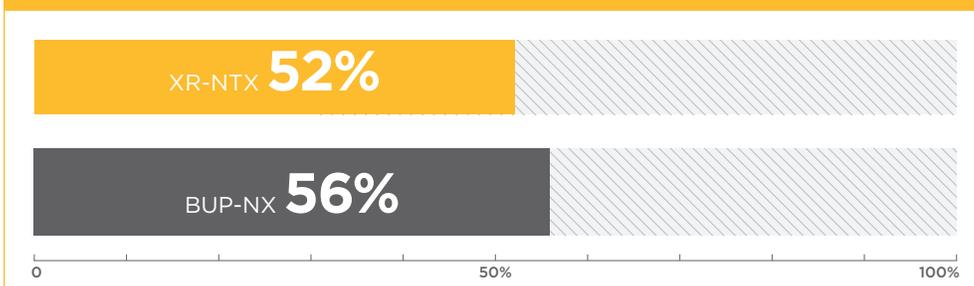
**Relapse (primary endpoint) in the per-protocol population**

In the per-protocol population, relapse events occurred in 52% of XR-NTX-treated patients and in 56% of BUP-NX-treated patients (**Figure 3**). The difference in relapse events in the per-protocol versus ITT populations was accounted for largely by a high incidence of early relapse due to XR-NTX induction failures.

The median time to relapse in this per-protocol population was 20.4 weeks in the XR-NTX group and 15.2 weeks in the BUP-NX group (HR, 0.92; 95% CI, 0.71 to 1.18;  $P=0.49$ ).

In this per-protocol population, 47% of patients inducted to XR-NTX (96/204) and 43% of patients inducted to BUP-NX (115/270) completed 24 weeks of treatment (did not end medication early).

**Figure 3.** Opioid Relapse (Weeks 3-24) in the Per-Protocol Population



Odds ratio, 0.87; 95% confidence interval, 0.60 to 1.25;  $P=0.44$ . BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

**IMPORTANT SAFETY INFORMATION**

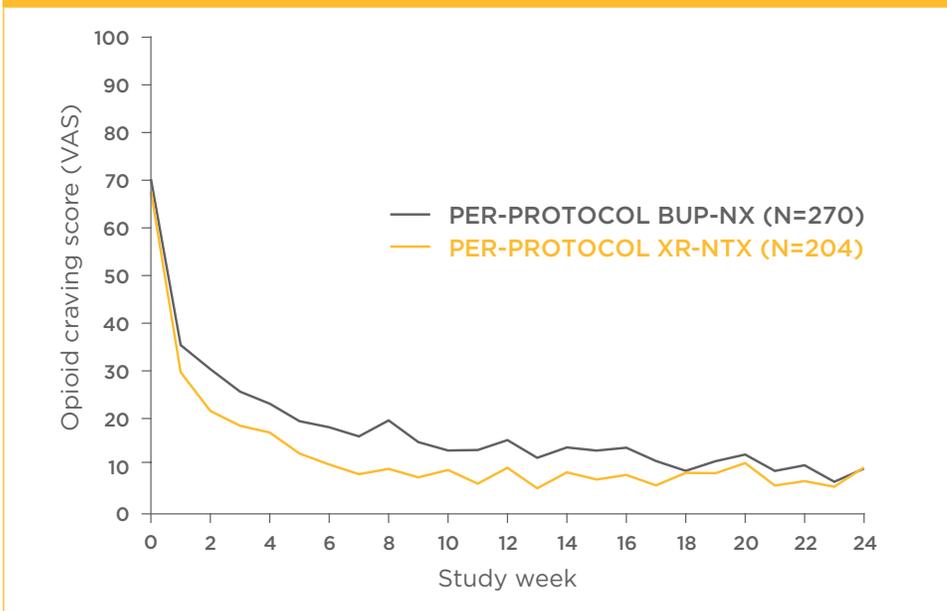
**WARNINGS AND PRECAUTIONS (cont.)**

**Injection Site Reactions:**

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Inadvertent subcutaneous/adipose layer injection of VIVITROL may increase the likelihood of severe injection site reactions.
- Select proper needle size for patient body habitus, and use only the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

**Please see Important Safety Information for VIVITROL throughout this newsletter. Please see Prescribing Information and Medication Guide. Review the Medication Guide with your patients.**

**Figure 4.** Self-Reported\* Opioid Craving



\*Reported using an opioid-craving visual analog scale (VAS), range 0-100. BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

### Secondary endpoint (craving)

Subjective, self-reported opioid craving declined rapidly from baseline in both treatment groups. Opioid craving was initially less with XR-NTX than with BUP-NX ( $P=0.0012$ ) but converged by Week 24 ( $P=0.20$ ) (Figure 4).

### Secondary endpoint (safety)

The proportion of participants reporting adverse events and serious adverse events did not differ between treatment groups, with the exception of injection site reactions among XR-NTX-treated patients (see Table 2 on page 6). All of the injection site reactions in the XR-NTX group were of minor to moderate severity. Five fatal overdoses occurred, in 2 participants treated with XR-NTX and in 3 participants treated with BUP-NX.

**This is not a complete list of adverse events for VIVITROL. Please see Important Safety Information and full Prescribing Information for additional safety information.**

(Continued from page 4)

### Commentary from the Steering Committee

#### Q: Any final words about medication-assisted treatment?

**Dr. Thomas Kosten:** It's important to offer patients a full array of treatment options, and these studies indicate that both extended-release naltrexone and buprenorphine-naloxone can be effective options for properly selected patients.

**Dr. Genie Bailey:** Extended-release naltrexone can be an effective medication for appropriate patients. But whatever the treatment approach used, the big challenge is keeping patients in recovery.

**Linda Frazier:** There's no magic bullet, and it's difficult regardless of the medication used. Regarding extended-release naltrexone, it's important to understand who's most appropriate for it and how best to manage the induction process. ■

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS (cont.)

#### Precipitation of Opioid Withdrawal:

- When withdrawal is precipitated abruptly by administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization, and in some cases, management in the ICU.
- To prevent occurrence of precipitated withdrawal, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment:
  - An opioid-free interval of a minimum of 7-10 days is recommended for patients previously dependent on short-acting opioids.
  - Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.

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**Table 2. Adverse Events and Serious Adverse Events**

	XR-NTX group (n=283)		BUP-NX group (n=287)	
	All	Serious	All	Serious
Treatment-emergent adverse events				
Participants with one or more treatment-emergent adverse event*	111 (54%)	29 (14%)	141 (52%)	29 (11%)
Number of treatment-emergent adverse events	247	39	334	35
Study medication discontinued due to adverse event	6		8	
Type of treatment-emergent adverse event				
Injection site reaction, mild or moderate	46		NA	
Gastrointestinal	34		59	
Psychiatric disorders	30	9	29	11
Injury, poisoning, and procedural complications	23		25	
Infections and infestations	22	5	27	6
Nervous system disorders	22		28	
Pregnancy		3		4
Death		3		4
Overdose Events	All	Per-protocol	All	Per-protocol
Participants with one or more overdose event	15 <sup>†</sup>	9 <sup>‡</sup>	8 <sup>†</sup>	7 <sup>‡</sup>
Number of overdose events	18 <sup>§</sup>	10	10 <sup>§</sup>	9
Fatal overdose events	All	Per-protocol	All	Per-protocol
Number	2	2	3	3

\*Treatment-emergent is defined as any adverse event that occurred after the study day of induction for those participants inducted onto study medication.

<sup>†</sup>P=0.14 (Fisher's exact).

<sup>‡</sup>P=0.31 (Fisher's exact).

<sup>§</sup>Four participants reported more than 1 overdose event. Three of the 4 participants were randomly assigned to XR-NTX (2 were induction failures, 1 was successfully inducted); each reported 2 overdose events. One of the 4 was randomly assigned to BUP-NX (successfully inducted) and reported 3 overdose events. None of these 9 overdoses was fatal BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

## Conclusion

The authors concluded that although it was more difficult to initiate patients onto XR-NTX than onto BUP-NX (which negatively affected overall relapse rates with XR-NTX), both medications were equally safe and effective once initiated. They also noted that these findings of noninferiority align with the results of the Norwegian study by Tanum et al (see page 7).

## Study Limitations

Study sites varied in detoxification protocols and length of inpatient stay. Ease of induction is a well-known limitation of XR-NTX compared to BUP-NX. A real-world effectiveness study such as X:BOT includes more sources of bias than a tightly managed efficacy study but potentially has higher generalizability.

# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS (cont.)

### Precipitation of Opioid Withdrawal (cont.):

- If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.
- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

### Hepatotoxicity:

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

**Please see Important Safety Information for VIVITROL throughout this newsletter.**

**Please see Prescribing Information and Medication Guide.**

**Review the Medication Guide with your patients.**

# Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial.<sup>2</sup>

Tanum L et al. *JAMA Psychiatry*. December 2017.

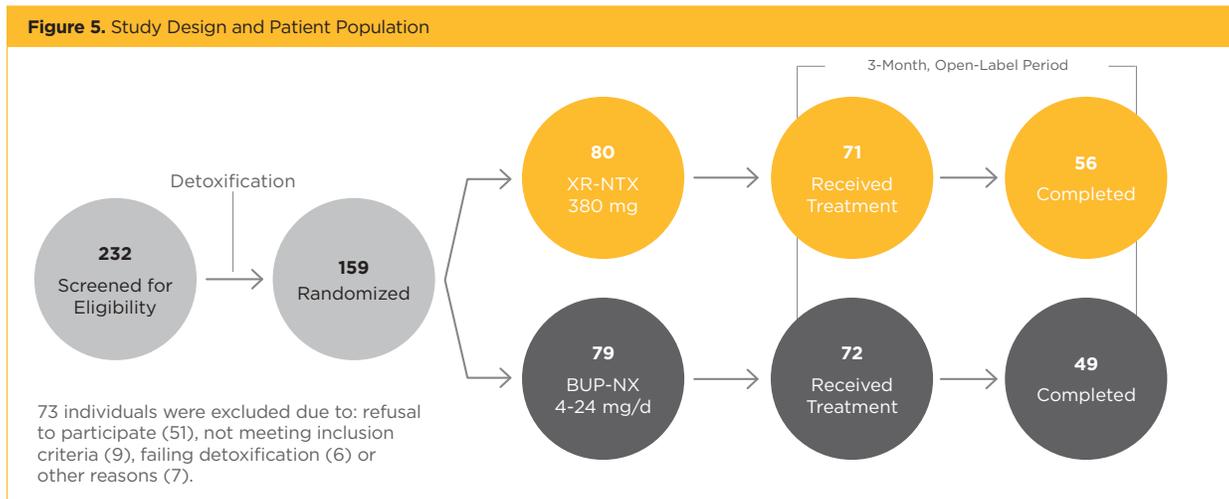
## Design

This Norwegian study was a 12-week, multicenter, outpatient, open-label, randomized, clinical noninferiority trial comparing the effectiveness of injectable extended-release naltrexone (XR-NTX) with daily oral buprenorphine-naloxone (BUP-NX) for the treatment of opioid dependence. Because this study was not blinded, participants in each treatment group knew which medication they were receiving.

The study was supported by unrestricted grants from the Research Council of Norway and the Western Norway Regional Health Authority. Financial support was also received from the Norwegian Centre for Addiction Research at the University of Oslo and from Akershus University Hospital. The funding organizations had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Alkermes, Inc., was allowed to comment on the manuscript before submission for publication and supplied XR-NTX for the study.

All patients were 18 years to 60 years of age and met *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*, criteria for opioid dependence. A total of 232 patients were recruited for the study from outpatient addiction clinics and detoxification units. Patients were excluded if they were pregnant or breastfeeding, had other drug or alcohol dependence, or had serious somatic or psychiatric illness interfering with participation. After screening and inclusion, participants were referred to a detoxification unit and randomized to treatment after detoxification (see **Figure 5**).

Of the original 232 subjects, 159 were randomized to receive either daily oral flexible-dose BUP-NX 4 mg/day to 24 mg/day (n=79) or XR-NTX 380 mg given intramuscularly every fourth week (n=80). All participants received weekly UDTs and were asked to attend standard drug counseling. However, no behavioral interventions could be initiated.



BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS (cont.)

#### Depression and Suicidality:

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

#### When Reversal of VIVITROL Blockade Is Required for Pain Management:

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

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## PRIMARY ENDPOINTS

The researchers sought to determine whether XR-NTX was noninferior to BUP-NX via the measurement of 3 primary endpoints: the number of days of use of heroin and other illicit opioids, the trial completion rate, and the proportion of UDTs that were negative for illicit opioids. The weekly UDTs were calculated as the number of opioid-negative urine drug screens divided by the total number of attended tests. For all participants, missing UDTs were considered positive for opioids.

Table 3. Demographics and Baseline Clinical Characteristics		
	Intention to Treat (N=159)	
	Extended-release Naltrexone (n=80)	Buprenorphine-Naloxone (n=79)
Age, years	36.4 (8.8)	35.7 (8.5)
Male	61 (76.3%)	54 (68.4%)
Female	19 (23.6%)	25 (31.6%)
White	72 (90%)	70 (88.6%)
Heavy opioid use, years	8.9 (7.8)	9.6 (10.5)
Heroin use, years	6.9 (5.8)	6.7 (5.2)
Other illicit opioid use, years	2.4 (5.1)	3.2 (7.0)
Heroin use during past 30 days	7.6 (11.0)	12.0 (12.9)
Other illicit opioid use during past 30 days	8.2 (11.1)	14.5 (13.2)

Data are mean (standard deviation) or number (%).

## Results

Demographic data for the 159 randomized patients are shown in **Table 3**. The population was about 70% male and about 90% white and had about 9 years of heavy opioid use on average.

With respect to days of use of heroin and other illicit opioids, treatment with XR-NTX showed noninferiority to BUP-NX. For XR-NTX compared with BUP-NX, the mean difference in days of heroin use was -3.2 (95% CI, -4.9 to -1.5;  $P < 0.001$ ) and the mean difference in days of other illicit opioid use was -2.7 (95% CI, -4.6 to -0.9;  $P < 0.001$ ; see **Figure 6** on page 9).

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS (cont.)

#### Eosinophilic Pneumonia:

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

#### Hypersensitivity Reactions:

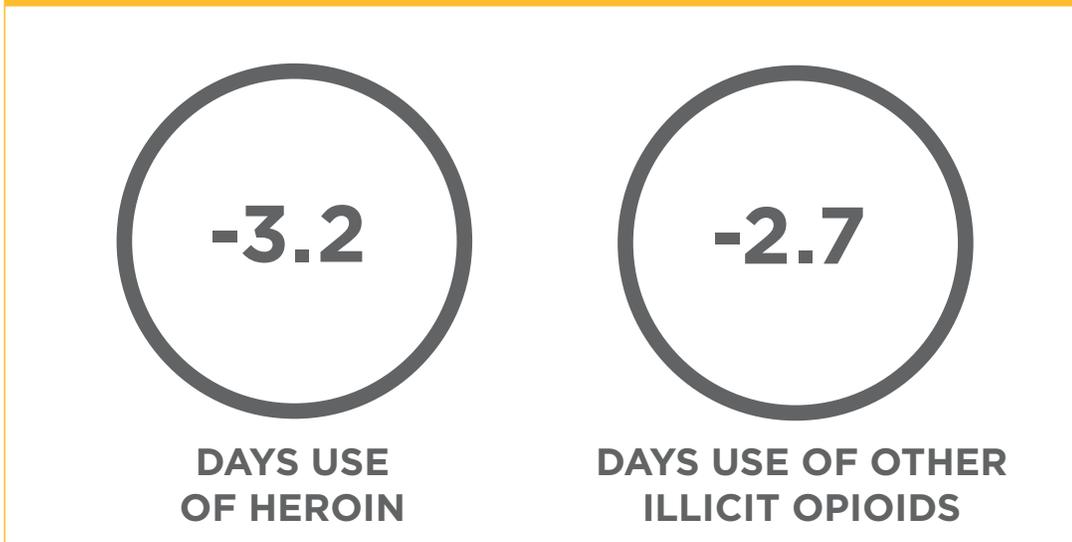
- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

#### Intramuscular Injections:

- As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

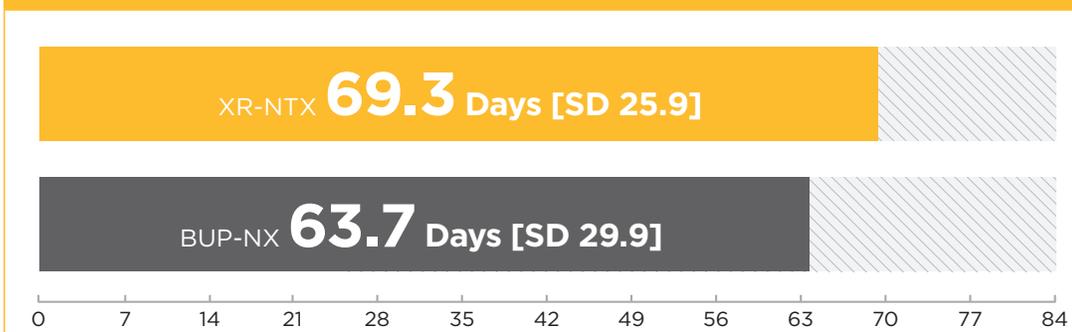
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**Figure 6.** Mean Difference in Opioid Use, XR-NTX vs BUP-NX



BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

**Figure 7.** Study Retention Time for XR-NTX vs BUP-NX



$P=0.33$ , log-rank test.  
BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone; SD, standard deviation.

XR-NTX also showed noninferiority to BUP-NX with respect to treatment retention at the end of the study. Specifically, the proportion of participants retained in the XR-NTX group ( $n=71$ ) was noninferior to that in the BUP-NX group ( $n=72$ ) (difference,  $-0.1$ ; 95% CI,  $-0.2$  to  $0.1$ ;  $P=0.04$ ). In addition, the percentage of patients who completed the 12 weeks of treatment was 70% ( $n=56$ ) in the XR-NTX group and 62% ( $n=49$ ) in the BUP-NX group. The retention time in days is shown in **Figure 7**.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS (cont.)

#### Alcohol Withdrawal:

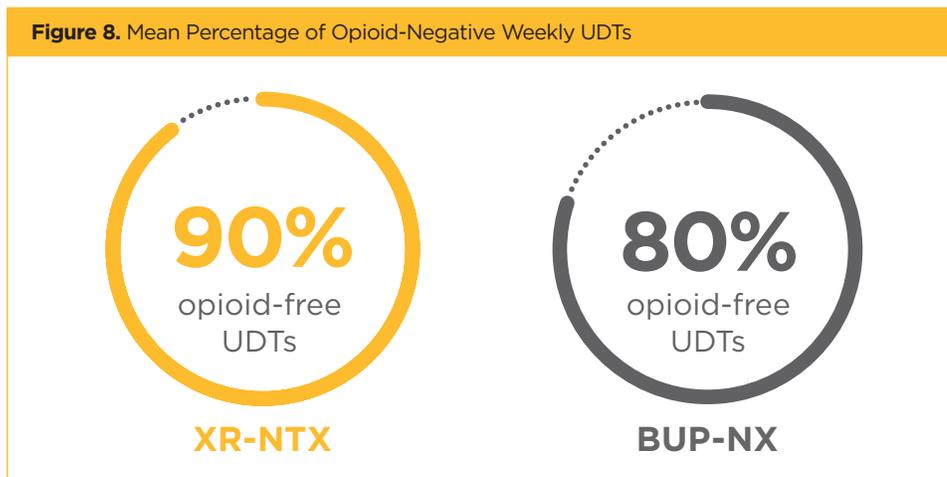
- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

#### ADVERSE REACTIONS

- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in  $\geq 5\%$  and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), arthralgia, arthritis, or joint stiffness, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.

Please see Important Safety Information for VIVITROL throughout this newsletter.  
Please see [Prescribing Information and Medication Guide](#).  
Review the [Medication Guide](#) with your patients.

XR-NTX showed noninferiority to BUP-NX in terms of the total number of opioid-negative UDTs as well. Specifically, treatment with XR-NTX was noninferior to BUP-NX regarding the group proportion of the total number of opioid-negative UDTs (mean [SD], 0.9 [0.3] and 0.8 [0.4], respectively; mean difference, 0.1; 95% CI, -0.04 to 0.2;  $P < 0.001$ ; **Figure 8**).



BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone; UDTs, urine drug tests.

## Conclusion

In this 12-week, multicenter, outpatient, open-label, randomized, clinical noninferiority trial, XR-NTX was found to be as effective as BUP-NX in maintaining short-term abstinence from heroin and other illicit opioids. The authors note that XR-NTX “should be considered as a treatment option for opioid-dependent individuals.”

## Study Limitations

This study was not blinded. Participants of each treatment group knew which medication they were receiving during the trial. For the study to have been blinded, it would have required placebo injections like the XR-NTX kits, and placebo tablets for BUP-NX. Patients would be able to determine their respective treatment quite quickly, given their

long experience with opioid use. Due to an increased risk of overdose in newly detoxified opioid users, the use of placebo and/or masking of medications was considered unethical.

**Please refer to the other newsletters in this series at [MeetingTheNeed.CurrentPsychiatry.com](http://MeetingTheNeed.CurrentPsychiatry.com) for more information about opioid dependence and medication-assisted treatment.**

### References

1. Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2018;391(10118):309-318.
2. Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry*. 2017;74(12):1197-1205.

## IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS (cont.)

- The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in  $\geq 2\%$  and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

**You are encouraged to report side effects to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.**



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**Vivitrol**<sup>®</sup>  
(naltrexone for extended-release injectable suspension)