Injectable extended-release naltrexone for opioid dependence: 3 studies

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Death by drug overdose is the number one cause of death in Americans 50 years of age and younger.[1] In 2016, there were 63,632 drug overdose deaths in the United States[2] Opioids were involved in 42,249 of these deaths, which represents 66.4% of all drug overdose deaths.[2] From 2015 to 2016, the age-adjusted rate of overdose deaths increased significantly by 21.5% from 16.3 per 100,000 to 19.8 per 100,000.[2] This means that every day, more than 115 people in the United States die after overdosing on opioids. The misuse of and addiction to opioids—including prescription pain relievers, heroin, and synthetic opioids such as fentanyl—is a serious national crisis that affects public health as well as social and economic welfare.

The gold standard treatment is medication-assisted treatment (MAT)—the use of FDA-approved medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach.[3] When it comes to MAT options for opioid use disorder (OUD), there are 3 medications, each with its own caveats.

Methadone is an opioid mu-receptor full agonist that prevents withdrawal but does not block other narcotics. It requires daily dosing as a liquid formulation that is dispensed only in regulated clinics.

Buprenorphine is a mu-receptor high affinity partial agonist/antagonist that blocks the majority of other narcotics while reducing withdrawal risk. It requires daily dosing as either a dissolving tablet or cheek film. Recently it has also become available as a 6-month implant as well as a 1-month subcutaneous injection. Buprenorphine is also available as a combined medication with naloxone; naloxone is an opioid antagonist.

Naltrexone is a mu-receptor antagonist that blocks the effects of most narcotics. It does not lead to dependence, and is administered daily as a pill or monthly as a deep IM injection of its extended-release formulation.

The first 2 medications are tightly regulated options that are not available in many areas of the United States. Naltrexone, when provided as a daily pill, has adherence issues. As with any illness, lack of adherence to treatment is problematic; in the case of patients with OUD, this includes a high risk of overdose and death.

The use of injectable extended-release naltrexone (XR-NTX) may be a way to address nonadherence and thus prevent relapse. One of the challenges limiting naltrexone's applicability has been the length of time required for an "opioid washout" of the mu receptors prior to administering naltrexone, which is a mu blocker. The washout can take as long as 7 to 10 days. This interval is not feasible for patients receiving inpatient treatment, and patients receiving treatment as outpatients are vulnerable to relapse during this time. Recently, there

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Injectable, extended-release antagonist may be a way to help address nonadherence and prevent relapse

Table

Injectable extended-release naltrexone: 3 studies

Study	Design	Outcome
Tanum et al[4] (2017)	N = 159, outpatients with OUD randomized after detoxification to BUP-NX or XR-NTX for 12 weeks	XR-NTX was as effective as BUP-NX for maintaining short-term abstinence from illicit opioids
Lee et al[5] (2018)	N = 570, open label, patients with OUD randomized to BUP-NX or XR-NTX for 24 weeks	It was more difficult to initiate patients on XR-NTX than on BUP-NX, but once initiated, both medications were equally safe and effective
Sullivan et al[6] (2017)	N = 150, adults with OUD randomized to outpatient detoxification facilitated with BUP or NTX, followed by XR-NTX	Compared with those who received BUP-assisted detoxification, patients who received NTX-assisted detoxification were significantly more likely to be successfully inducted to XR-NTX

BUP: buprenorphine; BUP-NX: buprenorphine-naloxone; NTX: naltrexone; OUD: opioid use disorder; XR-NTX: injectable extended-release naltrexone

Clinical Point

Patients who have failed agonist treatment or have a less severe form of OUD are optimal candidates for XR-NTX

have been several attempts to shorten this gap through various experimental protocols based on incremental doses of NTX to facilitate withdrawal while managing symptoms.

When selecting appropriate candidates for NTX treatment, clinicians should consider individuals who are:

- not interested in or able to receive agonist maintenance treatment (ie, patients who do not have access to an appropriate clinic in their area, or who are restricted to agonist treatment by probation/parole)
- highly abstinence-oriented (eg, active in a 12-step program)
- in professions where agonists are controversial (eg, healthcare and airlines)
- detoxified and abstinent but at risk for relapse.

Individuals who have failed agonist treatment (eg, who experience cravings for opioids and use opioids while receiving it, or are nonadherent or diverting/misusing the medication), who have a less severe form of OUD (short history and low level of use), or who use sporadically are also optimal candidates for NTX. Aside from the relapse-vulnerable washout gap prior to induction, one of the concerns with antagonist treatments is treatment retention; anecdotal clinical reports suggest that individuals often discontinue antagonists in favor of agonists.

Several studies have investigated this by comparing XR-NTX with buprenorphine-naloxone (BUP-NX). Here we summarize 3 studies[4-6] to describe which patients might be optimal candidates for XR-NTX, its success in comparison with BUP-NX, and challenges in induction of NTX, with a focus on emerging protocols (***Table***).

1. Tanum I, Solli KK, Latif ZH, 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.

This study aimed to determine whether XR-NTX was *not inferior* to BUP-NX in the treatment of OUD.

Study design

- N = 159, multicenter, randomized, 12-week outpatient study in Norway
- After detoxification, participants were randomized to receive BUP-NX, 4 to 24 mg/d, or XR-NTX, 380 mg/month.

Outcomes

- Comparable treatment retention between groups
- Comparable opioid-negative urine drug screens (UDS)

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• Significantly lower opioid use in the XR-NTX group.

Conclusion

• XR-NTX was as effective as BUP-NX in maintaining short-term abstinence from heroin and other illicit opioids, and thus should be considered as a treatment option for opioid-dependent individuals.

While this study showed similar efficacy for XR-NTX and BUP-NX, it is important to note that the randomization occurred after patients were detoxified. As a full opioid antagonist, XR-NTX can precipitate severe withdrawal, so patients need to be completely detoxified before starting XR-NTX, in contrast to BUP-NX, which patients can start even while still in mild withdrawal. Additional studies are needed in which individuals are randomized before detoxification, which would make it possible to measure the success of induction.

2. Lee JD, Nunes, EV, 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.

This study evaluated XR-NTX vs BUP-NX among adults with OUD who were actively using heroin at baseline and were admitted to community detoxification and treatment programs. Although the study began on inpatient units, it aimed to replicate usual community outpatient conditions across a 24-week outpatient treatment phase of this open-label, comparative effectiveness trial. Researchers assessed the effects on relapse-free survival, opioid use rates, and overdose events.

Study design

• N = 570, multicenter, randomized, 24-week study in the United States

• Detoxification methods: no opioids (clonidine or adjunctive medications), 3- to 5-day methadone taper, and 3- to 14-day BUP taper

• Protocol requirement: opioid-negative UDS before XR-NTX induction

• XR-NTX induction success ranged from 50% at a short-methadone-taper unit to 95% at an extended-opioid-free inpatient program. Nearly all induction failures quickly relapsed

• More participants inducted on BUP-NX group than XR-NTX group (94% vs 72%, respectively).

Outcomes (once successfully inducted to treatment [n = 474])

• Comparable relapse events

• Comparable opioid-negative urine drug screens and opioid-abstinent days

• Opioid craving initially less with XR-NTX.

Conclusion

• It was more difficult to initiate patients on XR-NTX than BUP-NX, which negatively affected overall relapse rates. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

Regarding induction on NTX, patients must be detoxified and opioid-free for at least 7 days. If this medication is given to patients who are physically dependent and/or have opioids in their system, NTX will displace opioids off the receptor and precipitate a severe withdrawal (rather than a slow and gradual spontaneous withdrawal).

Several studies have examined the severity of opioid withdrawal (using Self Opioid Withdrawal Scale scoring) of patients undergoing detoxification with symptomatic management (eg, clonidine, loperamide, etc.), agonist-managed (eg, with a BUP taper), and without any assistance. As expected, the latter yielded the highest scoring and most uncomfortable experiences. Using scores from the first

Clinical Point

Patients must be detoxified and opioid-free for 7 days before receiving XR-NTX

Clinical Point

For suitable candidates, XR-NTX seems to be as efficacious as agonist treatment for OUD

2 groups, a threshold of symptom tolerability was established where patients remained somewhat comfortable during the process. During detoxification from heroin, administering any dose of NTX during the first 48 to 72 hours after the last use placed patients in a withdrawal of a magnitude above the limit of tolerability. At 48 to 72 hours, however, a very low NTX dose (3 to 6 mg) was found to be well tolerated, and withdrawal symptoms were easily managed supportively to accelerate the detoxification process. Several studies have attempted to devise protocols based on these findings in order to facilitate rapid induction onto NTX. The following study offers encouragement:

3. Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. Am J Psychiatry. 2017;174:459-467.

Study design

- N = 150 adults with OUD, randomized to outpatient opioid detoxification
- Patients were randomized to BUP- or NTX-facilitated detoxification, followed by XR-NTX
- BUP detoxification group underwent a 7-day BUP taper followed by a opioid-free week
- NTX group received a 1-day BUP dose followed by 6 days of ascending doses of oral NTX, along with clonidine and other adjunctive medications.

Outcomes

- NTX-assisted detoxification was significantly more successful for XR-NTX induction (56.1% vs 32.7%).

Conclusion

- Compared with the BUP-assisted detoxification group, NTX-assisted detoxification appears to make it significantly more likely for patients to be successfully inducted to XR-NTX.

The evidence discussed here holds promise in addressing some of the major issues surrounding MAT. For suitable candidates, XR-NTX seems to be as efficacious an option as agonist (BUP) MAT, and its induction limitations could be overcome by using NTX-facilitated detoxification protocols.

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