

AN INTRODUCTION TO EXTENDED-RELEASE INJECTABLE NALTREXONE FOR THE TREATMENT OF PEOPLE WITH OPIOID DEPENDENCE

The U.S. Food and Drug Administration (FDA) approved extended-release injectable naltrexone (Vivitrol) in October 2010 to treat people with opioid dependence. This medication provides patients with opioid dependence the opportunity to take effective medication monthly, as opposed to the daily dosing required by other opioid dependence medications (i.e., methadone, buprenorphine, oral naltrexone). Extended-release injectable naltrexone was approved by FDA in 2006 to treat people with alcohol dependence.

Treatment of opioid dependence remains a national priority. According to the 2010 *National Survey on Drug Use and Health*, approximately 359,000 individuals reported either dependence on or abuse of heroin, and 1.92 million individuals reported either dependence on or abuse of prescribed painkillers.¹ *The Treatment Episode Data Set* (TEDS) reports that between 1998 and 2008 the percentage of individuals ages 12 and older who entered substance abuse treatment because of pain reliever abuse increased more than fourfold—from 2.2 percent to 9.8 percent.²

This *Advisory* provides behavioral health professionals—including substance abuse treatment specialists—and primary care medical providers (who treat people with opioid dependence) with an introduction to extended-release injectable naltrexone. It includes succinct information about extended-release injectable naltrexone, how it compares with other medication-assisted treatment (MAT) options, and clinical strategies that may be used to select, initiate, and administer treatment.

What Role Can Extended-Release Injectable Naltrexone Play in the Treatment of Opioid Dependence?

Extended-release injectable naltrexone is another pharmacological tool that is approved for treatment of people with opioid dependence. Over the years, medications have been successful in treating many patients with opioid dependence. Methadone has been used to treat patients for decades and has been proven effective.³ However, methadone must be dispensed to the patient at a Substance Abuse and Mental Health Services Administration (SAMHSA)-certified opioid treatment program (OTP) facility—with daily doses provided at the clinic—until the patient is deemed stable enough to receive take-home doses. Barriers to accessing this treatment include limited geographical locations of OTPs, transportation difficulties, and policies that preclude the use of methadone.

Buprenorphine, approved in 2002 by FDA to treat opioid dependence, is available at OTPs but is most often prescribed by physicians in office-based settings. Thus, in theory, it can be more accessible than methadone. However, to prescribe buprenorphine, physicians need limited special training and so all physicians may not currently be able to prescribe it. Physicians also need to be granted a waiver by the U.S. Drug Enforcement Agency (DEA) from regulations that otherwise prohibit them from treating people with opioid dependence in office settings and, at maximum, can only treat up to 100 patients at a time. Currently, mid-level practitioners (e.g., nurse practitioners, physician assistants) are not eligible for DEA waivers to prescribe buprenorphine.

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Naltrexone can be prescribed by any healthcare provider who is licensed to prescribe medications. Special training is not required; the medication can be administered in OTP clinics. Practitioners in community health centers or private office settings can also prescribe it for purchase at the pharmacy. These factors may improve access to treatment for opioid dependence.

Naltrexone requires that patients be abstinent from opioids for a period prior to induction. Such abstinence can be difficult for patients to achieve. Retention in treatment has sometimes been problematic when patients are asked to adhere to daily doses of oral naltrexone.⁴ A monthly injection of naltrexone, instead of daily dosing, may improve patients' adherence to their medication regimens.^{5,6}

Extended-release injectable naltrexone has a higher pharmacy cost than buprenorphine and methadone, but some data suggest that its use may reduce inpatient admissions, emergency room visits, and other health system costs.⁷ Nonetheless, the higher pharmacy cost of extended-release injectable naltrexone may limit access for patients who lack health insurance or other financial resources.

How Does Extended-Release Injectable Naltrexone Differ From Other Forms of MAT for Opioid Dependence?

Both methadone and buprenorphine are controlled substances, whereas naltrexone is not. Methadone is an opioid agonist, buprenorphine is a partial opioid agonist, and naltrexone is an opioid antagonist.

Different types of opioid receptors—or molecules to which opioid compounds attach themselves and exert their effects—are present in the brain. Agonists are drugs that activate these receptors, binding to them and producing an effect. Opioids such as methadone, morphine, and heroin are full agonists and have the greatest abuse potential. Antagonists also bind to opioid receptors, but rather than producing an effect, they block the effects of opioid compounds. Partial agonists bind to the receptors and activate them, but not to the same degree as full agonists.⁸

Naltrexone has no abuse potential, whereas methadone and buprenorphine do. Further information about the pharmacology of methadone can be found in Treatment Improvement Protocol (TIP) 43: *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*.⁹ Additional information about buprenorphine is available in TIP 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*.⁸

Some physicians are reluctant to prescribe agonists to treat opioid dependence because of their treatment philosophies, difficulties in tapering patients off these medications, or the potential for illicit diversion of agonist medications.⁵ Physicians with these concerns may be more comfortable prescribing an antagonist, such as naltrexone, rather than agonists.

Exhibit 1 summarizes key differences between extended-release injectable naltrexone, buprenorphine, and methadone.

How Does Extended-Release Injectable Naltrexone Work?

Naltrexone is an opioid antagonist, a medication that binds to and effectively blocks opioid receptors.^{8,10} It prevents receptors from being activated by agonist compounds, such as heroin or prescribed opioids, and is reported to reduce opioid cravings and to prevent relapse.^{11,12} Patients need to be informed that this medication will prevent them from feeling the euphoric effect or pain relief they previously felt when they took an opioid.^{10,13,14}

Are There Safety Concerns About Extended-Release Injectable Naltrexone?

Risk of accidental opioid overdose and death

Accidental overdoses and overdose-related deaths have occurred among patients who have taken opioids while being treated for opioid dependence with naltrexone-containing products—including both the extended-release injectable formulation and the daily oral formulation.^{15,16} Overdoses and overdose-related deaths are also a risk with

agonist therapies. No comprehensive mortality data are yet available about extended-release injectable naltrexone, but cases of fatal opioid overdose have been reported in patients who:

- Used opioids at or near the end of the 1-month dosing interval.
- Used opioids after missing a dose of extended-release injectable naltrexone.
- Attempted to overcome the opioid blockade.¹⁰

Patients who have been treated with extended-release injectable naltrexone may have reduced tolerance to opioids and may be unaware of their potential sensitivity to the same, or lower, doses of opioids that they used to take. If patients who are treated with extended-release injectable naltrexone relapse after a period of abstinence, it is possible that the dosage of opioid that was previously used may have life-threatening consequences, including respiratory arrest and circulatory collapse.¹⁰

Physicians have an obligation to educate patients who are treated with naltrexone-containing products about mortality risks that exist during and after leaving treatment for opioid dependence.^{13,17} Behavioral health providers may play a role in reminding patients of these risks. It is recommended that providers and patients develop a relapse prevention plan that includes strategies to decrease the risks if relapse occurs. If patients continue to use opioids during treatment, transition to agonist medications may be considered to reduce mortality risk, although these medications also have mortality risks.^{13,17}

Risk of precipitating withdrawal

Naltrexone displaces heroin or prescribed opioids from receptors to which they have bound, which can precipitate withdrawal symptoms.^{8,20} Therefore, complete detoxification from opioids before initiating or resuming extended-release injectable naltrexone is necessary to prevent withdrawal. At least 7–10 days without opioid use is recommended before beginning extended-release injectable naltrexone.^{10,16}

Exhibit 1: Key Differences Between Medications Used To Treat Patients With Opioid Dependence

Prescribing Considerations	Extended-Release Injectable Naltrexone	Buprenorphine	Methadone
Frequency of Administration	Monthly	Daily	Daily
Route of Administration	Intramuscular injection in the gluteal muscle by healthcare professional.	Oral tablet or film is dissolved under the tongue. Can be taken at a physician's office or at home.	Oral (liquid) consumption usually witnessed at an OTP, until the patient receives take-home doses.
Restrictions on Prescribing or Dispensing	Any individual who is licensed to prescribe medicine (e.g., physician, physician assistant, nurse practitioner) may prescribe and order administration by qualified staff.	Only licensed physicians who are DEA registered and either work at an OTP or have obtained a waiver to prescribe buprenorphine may do so.	Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the OTP.
Abuse and Diversion Potential	No	Yes	Yes
Additional Requirements	None; any pharmacy can fill the prescription.	Physicians must complete limited special training to qualify for the DEA prescribing waiver. Any pharmacy can fill the prescription.	For opioid dependence treatment purposes, methadone can only be purchased by and dispensed at certified OTPs or hospitals.

Sources: Adapted from ^{16,18,19}

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Adverse events

The most frequently reported adverse events include hepatic enzyme abnormalities, injection site pain, common cold symptoms, insomnia, and toothache. Nausea, vomiting, muscle cramps, dizziness, sedation, decreased appetite, and an allergic form of pneumonia have also occurred in people treated with extended-release injectable naltrexone.^{10,21}

Injection site reactions

Injection site reactions—including pain, hardness, swelling, blisters, redness, bruising, abscesses, and tissue death—have been reported to FDA. Some reactions are serious enough that surgery is needed.¹⁶

To reduce the risk of serious injection site reactions:

- Extended-release injectable naltrexone should be administered as an intramuscular injection into the gluteal muscle using the specially designed administration needle provided. It should never be administered intravenously, subcutaneously, or inadvertently into fatty tissues.
- Extended-release injectable naltrexone should be administered into alternating buttocks (sides of the patient) each month.
- Healthcare providers should consider alternate treatments for patients whose body size, shape, or posture makes it impossible to administer extended-release injectable naltrexone in the recommended location. Note that the needle provided is not a standard needle (see last bullet). It is not possible to substitute a standard needle of a longer length.
- Patients who develop injection site reactions that do not improve should be referred to a surgeon.
- The packaging of extended-release injectable naltrexone was changed in 2010. Both 1.5- and 2-inch needles are included for injecting the medication, to accommodate patients' different body sizes. Use the 2-inch needle for most patients and reserve the shorter needle for lean patients.^{10,16}

Liver adverse effects

The FDA requires warnings on formulations of naltrexone about possible liver adverse effects. The current product labeling for extended-release injectable naltrexone includes a warning about hepatotoxicity when the medication is given in more than the recommended dose. Use of the medication is contraindicated in patients with acute hepatitis or liver failure. The medication manufacturer states that the margin of separation between the apparently safe dose and the dose causing hepatic injury appears to be only fivefold or less.¹⁰ Extended-release injectable naltrexone should be discontinued if signs or symptoms of hepatitis develop (e.g., fatigue, loss of appetite, nausea, vomiting, abdominal pain, gray-colored bowel movement, joint pain, jaundice).¹⁰ Further research and postmarket surveillance are underway to determine any long-term effects of this formulation on the liver.

Which Patients May Benefit Most From Treatment With Extended-Release Injectable Naltrexone?

It is difficult to predict which medication will work for a particular patient with opioid dependence. Factors affecting a patient's treatment success with a medication may change over time or with subsequent treatment attempts. Extended-release injectable naltrexone benefits people with opioid dependence who are at risk for opioid use immediately after detoxification.⁶ People facing periods of greatly increased stress or other relapse risks (e.g., visiting places of previous drug use, loss of spouse, loss of job) may find they benefit from the reassurance of the blockade provided by the medication.^{11,13} People who have a short or less severe history of dependence may also want to consider injectable naltrexone.⁶ Still others may have to demonstrate to professional boards, supervisors, drug court judges, or other authorities that their risk of using a nonprescribed opioid is low and the extended-release formulation may provide an option that has reduced risk compared with other options. No definitive research is available that states which patients would most benefit from extended-release injectable naltrexone, but the following people may be good candidates for treatment.

People who have not had treatment success with methadone or buprenorphine

Depending on the reasons for treatment failure, people with opioid dependence who have not been successful with treatment with methadone or buprenorphine may benefit from extended-release injectable naltrexone.²²

People who have a high level of motivation for abstinence

People who are highly motivated to achieve and maintain abstinence from opioids may be good candidates for extended-release injectable naltrexone.^{12,23} This includes people who are required to demonstrate abstinence with drug screens, such as individuals in impaired healthcare provider programs, parolees, probationers, and airline pilots.²⁴ Preliminary results from an ongoing study of U.S. healthcare professionals with opioid dependence suggest that this treatment can be successful for up to 1 year.²⁵

People successful on agonists who wish to change their medication or patients not interested in agonist therapy to treat their opioid dependence

Some patients may be successful on agonist treatment and want continued pharmacologic help to prevent relapse but would prefer another type of treatment,²² while other patients may never be interested in agonist therapy. These types of patients could include individuals who:

- Feel they are discriminated against, or are embarrassed or ashamed, because they are on methadone maintenance or who previously experienced these emotions while undergoing methadone therapy.²⁶
- Would like to reduce the time devoted to daily or multiple OTP visits per week, as is often required for methadone treatment.¹³
- Prefer to receive office-based treatment in a primary medical care setting, rather than treatment in specialty clinics or treatment centers.^{24,26}

Adolescents or young adults with opioid dependence

Methadone or buprenorphine are not always available to treat young people with opioid dependence because of OTP facility policies or governmental regulations. However, the safety and efficacy of extended-release injectable naltrexone have not been established for patients who are younger than age 18, and use for this population is not approved by FDA. Only limited experience in treating this population with extended-release injectable naltrexone is reported in the literature.²⁶

Can Extended-Release Injectable Naltrexone Be Used With Behavioral Therapies?

For most patients with opioid dependence, medications alone are insufficient. Treatment in individual or group counseling sessions and participation in mutual-help programs are also needed. Patients have better treatment outcomes when naltrexone-based treatment is combined with behavioral therapies.^{4,6,27} The efficacy of extended-release naltrexone has been established when given in conjunction with behavioral support; it has not been studied as a sole component of treatment.

Healthcare providers should be ready to offer brief intervention if patients relapse during treatment of opioid dependence. Motivational interviewing and relapse prevention strategies may also enhance the effectiveness of pharmacological treatments.⁸

How Can Pain Be Treated During or After Extended-Release Injectable Naltrexone Treatment?

Pain management in people receiving all forms of MAT, including extended-release injectable naltrexone, can be challenging. Some people can be safely and effectively treated with nonpharmacologic remedies, such as physical therapy, massage, or acupuncture, as long as the injection site is protected. Pain relief may also be obtained from nonopioid topical medications, nonsteroidal anti-inflammatory agents, regional blocks,

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and nonopioid painkillers such as gabapentin and atypical antidepressants.¹³

Use of opioid-containing analgesics may aggravate preexisting addiction disorders and cause relapse. People with opioid dependence who require opioid therapy for chronic pain should be managed by pain management specialists. In light of its antagonist property, extended-release injectable naltrexone may not be appropriate for these patients.²²

Reversing blockade of opioid receptors

There are few clinical trial data available about reversing the opioid receptor blockade. When surgeries or procedures are planned for patients who use extended-release injectable naltrexone, it may be safest to delay the procedure until naltrexone blood levels are low enough to restore opioid receptor availability. The manufacturer of extended-release injectable naltrexone also suggests considering use of regional analgesia or nonopioid analgesics.¹⁰

In emergencies, it is possible for healthcare providers to reverse extended-release injectable naltrexone's opioid receptor blockade. However, higher than usual dosages of a rapidly acting opioid medication may be needed to achieve pain relief if a patient still has a tolerance to opioids. These higher dosages increase the risk of respiratory depression. Patients administered such high doses should be closely monitored by professionals trained in the use of anesthetic drugs, management of respiratory depression, and the performance of cardiopulmonary resuscitation.^{10, 16}

Patients who are treated with extended-release injectable naltrexone should be encouraged to wear medical alert jewelry or carry a disclosure card to help emergency personnel provide pain management safely when these patients are unconscious or cannot otherwise communicate.

Resources

Several publications are available free of charge from SAMHSA. The resources listed below can be ordered from SAMHSA's Publications Ordering Web page at <http://www.store.samhsa.gov>. Or call 1-877-SAMHSA-7 (1-877-726-4727) (English and Español). Publications can also be downloaded from the Knowledge Application Program Web site at <http://www.kap.samhsa.gov>.

Resources for professionals

Substance Abuse Treatment Advisory: Naltrexone for Extended-Release Injectable Suspension for Treatment of Alcohol Dependence. (2007). Volume 6, Issue 1. HHS Publication No. (SMA) 07-4267.

Substance Abuse Treatment Advisory: Emerging Issues in the Use of Methadone. (2009). Volume 8, Issue 1. HHS Publication No. (SMA) 09-4368.

Treatment Improvement Protocol (TIP) 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction.* (2004). HHS Publication No. (SMA) 07-3939.

TIP 43: *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs.* (2005). HHS Publication No. (SMA) 08-4214.

TIP 45: *Detoxification and Substance Abuse Treatment.* (2006). HHS Publication No. (SMA) 08-4131.

Resources for clients

The Facts About Naltrexone for Treatment of Opioid Addiction. (2009). HHS Publication No. (SMA) 09-4444.

Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends. (2009). HHS Publication No. (SMA) 09-4443.

Other Web resources for medical and health professionals

National Institute on Drug Abuse, NIDAMED

<http://www.drugabuse.gov/nidamed>

U.S. Food and Drug Administration

<http://www.fda.gov>

For specific information on extended-release injectable naltrexone: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s005s0101bl.pdf

For specific information on adverse injection site reactions: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug-SafetyInformationforPatientsandProviders/ucm103334.htm>

Notes

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