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# Advances in Opioid Antagonist Treatment for Opioid Addiction

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## Perspective on Opioid Antagonist Treatment for Addiction

Naltrexone, an opioid antagonist derived from the analgesic oxymorphone, was synthesized as EN-1639A by Blumberg and colleagues in 1967. Four years later, in 1971, naltrexone was selected for high-priority development as a treatment for opioid addiction by the Special Action Office for Drug Abuse Prevention, an office created by President Nixon and put under the leadership of Dr Jerome Jaffe.

### Extinction Model

The rationale for the antagonist approach to treating opioid addiction had been advanced by Dr Abraham Wikler a decade earlier, based largely on the extinction model explored in animal behavioral studies. It was believed that by blocking the euphorogenic effects of opioids at the opioid receptors, opiate use would become less rewarding and less desirable and, in time, opiate users—animals and humans—would learn to stop.

Unfortunately humans do not always behave like animals. When an animal keeps pressing a lever and gets no rewarding drugs, it stops pressing the lever; however, when human addicts discover that their medication keeps them from getting high, they stop taking their medication instead. It seems that human beings make decisions to use or not use drugs based on a cognitive process. Even the worst of compulsive gamblers will not put money into a slot machine that has an “out of order” sign on it. The decision and action are not from a gradual process—as in extinction—but are immediate; it is a matter of cognition, not extinction. Even though the compulsive gambler may claim to have no control over his gambling habit, it is obvious that he does have control; he stops putting money into the machine the instant he learns that there is no payoff; extinction does not apply here.



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## Naltrexone

### Properties

Pharmacologically, naltrexone is almost an ideal medication and it was once regarded as such.

- It completely blocks the euphoric effects of opioids.
- It has no reinforcing effects of its own.
- It is relatively safe and easy to take, with few side effects.

Unfortunately, these favorable clinical properties did not translate into clinical success.

### Clinical Experience

A major reason for its lack of clinical success was poor medication compliance, so much so that the pharmacologically "perfect drug" was becoming a "victimless cure." Dr Richard Resnick, a psychiatrist and an early clinical investigator, noted that naltrexone is ego-dystonic to an addict. Dr David Smith, who founded the Haight-Ashbury Free Clinic, said "addicts do not take naltrexone because they can't get high." My old friend and colleague Don Wesson simply notes that addicts do not like to take naltrexone because it ruins their lives.

Still, it is probably too pessimistic to say that the early clinical experience with naltrexone was a complete failure; there were certain special groups of patients who did very well with oral naltrexone treatments: Physicians, nurses, pharmacists, and lawyers who were under threat of losing their professional licenses. Prisoners on work release and parolees also seemed to do well. A common thread among these groups includes their having something to lose, the immediacy of the consequences of failure to comply with treatment, and, for the professionals at least, their knowledge that life could be quite different.

### Agonist Versus Antagonist

Our enthusiasm for naltrexone despite early clinical failure can be explained, in part, by the treatment success in select subgroups of patients as noted; additional support for naltrexone development came from societal attitude toward addicts and addiction. The US social structure of authorities, policymakers, funding agencies, the public, and even clinicians had all been ambivalent about full agonist pharmacotherapy (methadone) from the very beginning, and the antagonist option held great appeal. Methadone treatment in the United States is the most regulated medical practice. We were never comfortable with giving our addicted patients something so close to their drug of abuse, clinical benefit and lives saved notwithstanding. We were determined to wean our patients off their drug of abuse or at least treat them with something they could not use to get high. Naltrexone looked like the answer.

### Noncompliance with Naltrexone and Subsequent Opioid Overdose

The major problem with oral naltrexone is noncompliance, and that noncompliance and patient-initiated termination of naltrexone therapy have been linked with opioid overdose at a rate higher than occurs with methadone treatment,[1,2] possibly because of the decreased

tolerance or receptor supersensitivity after ongoing opioid receptor blockade. So, although the antagonist approach is certainly plausible and has worked to treat addiction in controlled experimental conditions and in limited practice with select patient groups, the fact remains that oral naltrexone did not work for most opioid addicts, especially because of poor medication adherence. The answer to poor adherence to oral naltrexone was, therefore, an extended-release formulation as depot naltrexone.

## Depot Naltrexone

### Development

Despite naltrexone's lack of early clinical success, investigators and policymakers as well as funding agencies reasoned that what was needed was a long-acting formulation of the medication that can be given to patients and, once administered, remains in effect regardless of patients' desires or behaviors; hence, the development of depot naltrexone, with the first attempts dating back to the 1970s. The idea was to produce a preparation that would last from weeks to months, thus relieving the addicted patients of their need to make daily decisions to take an antagonist medication that keeps them from getting high. In addition to the fact that patients are generally not keen on taking the medication, developing a reliable extended-release product was not technologically simple. It took nearly 30 years to get the first US Food and Drug Administration (FDA)-approved form of extended-release naltrexone to the market.

While the scientists were busy developing a more ideal formulation of naltrexone for opioid addicts, no one seems to have figured that perhaps we should ask our patients whether they would like to have such a medication. Patient compliance was poor in the early clinical trials with naltrexone as a liquid, which was very bitter. A tablet formulation did not improve compliance. Administration of naltrexone as an intramuscular injection may be less onerous because it occurs only once a month. Early-phase clinical experience with depot naltrexone has not wholly resolved the question about patients' acceptance of or disinclination toward extended-release naltrexone by injection, because we are seeing limited uptake in practice.

### Studies for the Treatment of Opioid Addiction

Research on depot naltrexone formulations has found positive results. As demonstrated by Comer and others,[3–5] 384 mg naltrexone delivered in extended-release depot formulation blocked the reinforcing, subjective, and physiologic effects of up to 25 mg of heroin, and provided consistent plasma levels for approximately 30 days.[6–8] Importantly, at this dose, naltrexone resulted in retention of more than 80% of patients in treatment at 6 weeks versus 40% for placebo.[4] In comparison with the oral formulation, patients on depot naltrexone showed significantly higher rates of abstinence and better treatment outcomes at 12-month follow-up.[9] Adverse events were minimal and limited to local responses at the injection site.[10]

Extended-release naltrexone preparation was approved by the FDA in October 2010, based predominantly on data from a large trial set in Russia, where no agonist pharmacotherapy is available for treatment of opioid addiction. In the approved formulation (XR-NTX [Vivitrol]; Alkermes, Inc., Waltham, MA, USA), naltrexone is slowly released from

microspheres composed of a polymer, poly-(D, L-lactide-coglycolide), which is also used in dissolvable surgical sutures. With its approval came a surge of interest in antagonist treatment for opioid addiction because the medication offered an alternative to the mainstay of methadone maintenance and the rapidly increasing popularity of buprenorphine, a partial agonist. XR-NTX has not yet commanded a staunch following, although its use is perhaps on a modest upswing. The focus of this article is on the use of XR-NTX, the only approved depot naltrexone medication available for addiction treatment; the basic information will be generally applicable to other extended-release depot forms as they come to market in North America and internationally.

## Lessons from the Large-Scale Trial of XR-NTX for Opioid Addiction

Study data from the industry-sponsored trial in Russia were provided to the FDA in the summer of 2010. These data formed the foundation for the FDA approval of XR-NTX to treat opioid addiction and prevent relapse in patients who have been detoxified from opioids. The study results were published in August 2011,[11] and the article provided limited guidance for clinicians who would bring XR-NTX into clinical practice. However, clinicians interested in using XR-NTX in treating opioid addiction still face a steep learning curve. The Russian study and findings from previous work made evident the following:

- XR-NTX improves treatment retention and substance use outcomes (eg, more weeks abstinent, fewer opioid-positive urine analyses) relative to placebo, which may be partially attributable to better engagement in behavioral therapies via more attendance.
- The 6-month regimen may not suit everybody; only 57.9% of the XR-NTX patients and 41.9% of the placebo patients received all 6 monthly injections.
- The placebo group did not fare so poorly, notwithstanding the significant difference in outcomes; of the 250 participants (126 in the active condition, 124 in the placebo condition), 45 patients on XR-NTX had “total confirmed abstinence” (all urine tests negative for opioids) compared with 28 in the placebo group. One could argue for a strong placebo effect or a strong counseling condition that helped the placebo group to remain somewhat free of opioids; however, XR-NTX was superior to placebo in its ability to prevent relapse to opioid use.
- XR-NTX has an anti-craving effect; opioid craving scores were significantly reduced over the 24-week course of treatment relative to placebo, beginning at week 8 and persisting for the duration of the trial.

A larger trial with more comprehensive measures of patient characteristics conceivably would be able to tease outpatient typologies that may be most suited to XR-NTX and whose outcomes might be expected to be optimized as a result of engaging in depot antagonist pharmacotherapy. The Russian study found “no significant relation … between age, sex, or duration of opioid dependence and the rate of opioid-free urine tests” with a stable treatment effect across baseline variables. No notable findings emerged regarding safety or tolerability, although more information on the reason for many participants declining XR-NTX injections would have been helpful to inform future clinical use; perhaps the dataset can be reanalyzed to reveal possible associated characteristics to inform practice. For now,

other research and clinical reports must stand as the source of limited information on the use of XR-NTX.

## Extended-Release Depot Naltrexone in Current Practice

### Primary Pharmacotherapy for Opioid Addiction

**Detoxification required—**Unlike methadone and buprenorphine, which with certain precautions can be given to opioid-addicted patients who are actively using illicit opioids, an antagonist can only be administered to patients who are not physically opioid dependent. This means most patients need to be "detoxified" to become opioid free before inducting them onto naltrexone. Unfortunately, many patients fail to complete detoxification and cannot begin antagonist treatment. The problem is troublesome enough with oral naltrexone, but it is much more serious an issue with the extended-release depot formulation because of its long duration of action and potential to precipitate prolonged opioid withdrawal.

Clinicians interested in using depot naltrexone in their practice need to learn to safely induct patients onto the medication. Detoxification can be done either in outpatient or inpatient settings, and a number of conventional methods are available. Although practiced by some clinicians, ultra-rapid detoxification under anesthesia is not recommended given the added risks of serious adverse events and lack of demonstrated benefit over other naltrexone induction methods.[12]

To initiate treatment with XR-NTX, steps should be taken to ensure that the patient is sufficiently free from physical dependence on opioids. These steps typically include confirmation of (1) absence of recent self-reported opioid use, (2) opioid-negative urine drug screen, and (3) tolerance of naloxone challenge test. According to package insert guidelines, patients should be opioid-free for at least 7 to 10 days before commencing XR-NTX treatment. However, rapid induction strategies have been utilized that incorporate the use of buprenorphine, clonidine, benzodiazepines, and other supportive medications; escalating doses of oral naltrexone may be incorporated to ensure absence of opioid withdrawal and facilitate initiation of XR-NTX treatment.

### Administration Challenges for Psychiatrists

The administration of XR-NTX to patients, although not particularly complicated, is time consuming and not a routine part of the practice for psychiatrists. The medication has to be kept refrigerated until ready for use, then prepared and shaken as instructed and administered. This usually requires the medication to be taken out of the refrigerator about 1 to 2 hours before the patient's appointment. If the patient fails to keep the appointment, the medication needs to be promptly returned to refrigeration, within a few hours. Moreover, clinicians are reminded about the need for careful preparation of the patient. Because many psychiatric clinicians find the detoxification/pre-induction procedures difficult or impossible to perform, most refer the process to colleagues of other specialties.

### Outcomes of Depot Naltrexone

It is intuitively tempting to want to compare treatment outcomes of depot naltrexone to agonist or partial agonist treatment (methadone or buprenorphine), even though they may serve very different patient populations. If one were to combine retention and abstinence as a composite outcome measure, depot naltrexone may yet compare favorably to agonist treatment; only time can tell. Such comparisons are not always useful or even fair; agonist treatment is not always available to certain patient groups, such as opioid-dependent physicians or nurses, who can do well with an antagonist medication.

### Side Effects of Naltrexone

The potential side effects of naltrexone include nausea, vomiting, worsening of depression, and suicidal thinking. When given in excessive doses, naltrexone carries a risk of hepatocellular injury, which is listed as a black box warning, though XR-NTX does not seem to have hepatotoxic effects at recommended doses. Still, it should be used cautiously in patients with active liver disease and is contraindicated in patients with acute hepatitis or liver failure. Injection site reactions may occur and may be characterized by pain, tenderness, erythema, induration, swelling, bruising, and pruritus. In some cases, reactions may be severe and may rarely require operative intervention.

XR-NTX blocks the effects of opioids for 28 days and, after cessation of treatment, patients may have reduced tolerance to opioids. Opioid use after treatment with XR-NTX, or the use of large amounts of opioids in an attempt to overcome the blockade, could result in opioid toxicity or potentially fatal overdose; however, these outcomes have not been observed in clinical trials of XR-NTX to date. Case reports have documented the potential to overcome mu blockade with opioids towards the end of the dosing interval, causing precipitated withdrawal upon subsequent administration of XR-NTX.[13]

## Combinations With Other Medications

Research on naltrexone in combination with other medications suggests many opportunities for studying mixed receptor activities in the treatment of opioid and other drug addictions (eg, increasing retention, relapse prevention, treatment for polysubstance abuse, pain management). Such combinations require careful evaluation by well-designed controlled clinical studies to understand the added therapeutic effects as well as safety issues.[14] The availability of XR-NTX represents a potentially valuable approach for replicating and improving studies done with oral naltrexone, because XR-NTX is likely to eliminate concern about medication compliance the adherence issue. Meanwhile, clinicians must balance the potential benefit against the added side effects and the potential for abuse of the added medications. Some of the most promising classes of medications that could be used in combination with XR-NTX are presented below.

### Antidepressants

Depression is among the most prevalent comorbid mental health condition among opioid-addicted individuals,[15] which provides rationale to combine depot naltrexone with antidepressants. Landabaso and associates[16] conducted a randomized trial of 112 heroin

addicts in Spain to test whether fluoxetine would enhance retention in a naltrexone treatment program. The investigators found that the combination of fluoxetine and naltrexone (n = 56) produced significantly greater retention than in patients given only naltrexone (n = 56). The findings show that placebo-controlled trials are warranted to assess further specific pharmacologic effects.

In Russia, Krupitsky and colleagues[17] used a randomized, placebo-controlled design to test the efficacy of oral naltrexone with or without fluoxetine for preventing relapse to heroin addiction and for reducing HIV risk, psychiatric symptoms, and outcome (n = 280). All patients received drug counseling with parental or significant-other involvement to encourage adherence. At the end of 6 months, 43% of subjects in the naltrexone/fluoxetine group, 36% in the naltrexone/placebo–fluoxetine group, 21% in the placebo-naltrexone/fluoxetine group, and 10% in the placebo–naltrexone/placebo–fluoxetine group remained in treatment and had not relapsed. Although adding fluoxetine did not improve the overall outcomes, women receiving naltrexone/fluoxetine showed a trend toward an advantage when compared with women receiving naltrexone/placebo–fluoxetine. Like other studies, dropout is a concern, which calls for randomized trials of long-acting depot naltrexone to determine whether it would improve retention.[17]

## γ-Aminobutyric Acid Agonists

One factor that may contribute to noncompliance or relapse among opioid-dependent individuals undergoing naltrexone treatment has been reported to be related to stress, drug cue–induced cravings, and arousal responses or insomnia. Therefore, pharmacologic interventions that specifically target the negative affectivity, which co-occurs with drug cue– and stress–induced craving, could be of benefit in improving naltrexone treatment outcomes for opioid dependence.[18,19] Stella and co-workers[19] evaluated whether naltrexone combined with the benzodiazepine prazepam was more effective than naltrexone alone in keeping patients opioid free. Relapse rates over 6 months in 56 opioid-dependent subjects were compared among 4 groups with an equal sample size. Group 1 did not receive pharmacologic treatment (control), group 2 received naltrexone alone, group 3 received naltrexone plus placebo, and group 4 received naltrexone plus prazepam. Ten patients in group 1 relapsed within 3 months, 1 after 6 months, and 3 remained opioid free. Six patients in group 2 relapsed within 3 months, 2 after 6 months, and 6 remained opioid free. Seven patients from group 3 relapsed within 3 months, 1 after 6 months, and 6 remained opioid free. In group 4, 1 patient relapsed within 3 months and 1 patient after 6 months; 12 patients of this group remained opioid free. More patients in the naltrexone plus prazepam group also remained cannabis free than the other groups. The authors concluded that combination treatments seem to be a promising strategy in naltrexone long-term treatment of opioid addiction.

## α-Adrenergic Agents

One approach with naltrexone aims to enhance the therapeutic effect for treating opioid addiction by the additive or synergistic effects of the drug combination. Naltrexone has, for instance, been combined with the *α*-adrenergic agents (eg, lofexidine and guanfacine) to

take advantage of the latter medications' ability to reduce symptoms of opioid withdrawal.[20,21]

Sinha and colleagues[22] examined whether lofexidine would decrease stress- and cue-induced opioid craving and improve opioid abstinence in naltrexone-treated, opioid-dependent individuals. Eighteen opioid-dependent patients were stabilized for 4 weeks with naltrexone (50 mg daily) and lofexidine (2.4 mg bid) before entering a 4-week randomized, double-blind, placebo-controlled discontinuation study where 1 group continued on lofexidine for an additional 4 weeks, and the second was tapered to placebo (lofexidine–naltrexone vs placebo–naltrexone). Results indicated that the lofexidine–naltrexone group had higher opioid abstinence rates and improved relapse outcomes than the placebo–naltrexone group, and that lofexidine–naltrexone patients had significantly lower heart rates and an attenuated stress and drug cue-induced opioid craving response in the laboratory compared with the Placebo-naltrexone group. Sinha and associates concluded that combination therapies targeting both drug-related reinforcement (naltrexone) and stress- and cue-related aspects of drug seeking could be beneficial in reducing relapse in addictive disorders.

In Russia, a large, randomized, double-blind, double-dummy, placebo-controlled, 4-cell study of naltrexone and guanfacine among 300 opioid-dependent patients is being conducted to examine the additive effect of guanfacine on preventing relapse among opioid-dependent patients.[23] When completed, results should provide information useful for informing naltrexone research.

## Opioid Agonists

Opioid addiction is frequently comorbid with other substance abuse, particularly with alcohol and cocaine use disorders.[24] Buprenorphine has been found to reduce cocaine use in opioid-dependent patients.[25] Preclinical evidence suggests possible beneficial effects of $\kappa$-opioid receptor antagonist in treating cocaine addiction, and Rothman and co-workers[26] proposed and explored the combination of naltrexone and buprenorphine as a functional $\kappa$-opioid receptor antagonist to reduce dysphoric symptoms associated with opioid withdrawal and cocaine use in a sample of 15 opioid-dependent individuals. Five patients (33%) completed the 3-month study; 4 were abstinent from opioids and cocaine for the entire study and 1 was abstinent from opioids and cocaine for the last 9 weeks. Rothman and colleagues[26] concluded that the positive response to treatment exceeded that expected from naltrexone alone (90% dropout).

Subsequently, Gerra and co-workers[27] examined naltrexone and buprenorphine combination in the treatment of opioid dependence in a nonrandomized, 3-month, observational study. The buprenorphine/naltrexone group showed a lower rate of positive urines for opioids and cocaine metabolites and more improvement in psychological symptoms (irritability, depression, tiredness, psychosomatic symptoms, and craving) than the naltrexone-only group.

These findings suggest a theoretical rationale for further investigation of the efficacy of the naltrexone and buprenorphine combination in treating opioid and cocaine addictions.

Additionally, oral naltrexone and XR-NTX have been approved by the Food and Drug Administration for the treatment of alcoholism. The beneficial effects of mixed receptor activities of the buprenorphine plus naltrexone combination on opioid and alcohol addictions may warrant research.[28] Given that availability of XR-NTX, these studies lend some support for evaluating the combination of buprenorphine and long-acting depot naltrexone in treatment for polysubstance addictions.

## Opioids and Low Doses of Opioid Receptor Antagonists

Preclinical and clinical studies have shown that co-treatments of opioids and ultra-low doses of opioid receptor antagonists (eg, naltrexone, naloxone) may enhance the efficacy of opioid analgesics and simultaneously attenuate opioid tolerance and dependence.[29] Findings from a study of 60 patients showed that a low-dose infusion of naloxone in patient-administered morphine sulfate was associated with fewer morphine-related side effects and reduced postoperative opioid requirements.[30] However, application of such co-treatment procedures with low-dose opioid antagonist plus morphine to chronic pain patients who are also dependent on prior use of opioid analgesics requires careful monitoring to avoid possible transitory opioid withdrawal symptoms, which might be elicited by administration of low doses of opioid antagonists.[29]

Of note, oxycodone plus an ultra-low dose of naltrexone (Oxytrex; Pain Therapeutics, Inc., Austin, TX, USA) was developed as an alternative to oxycodone to treat moderate to severe chronic pain without increasing side effects. Using an animal model, Largent-Milnes and associates[31] proposed that Oxytrex presents a novel approach to neuropathic pain therapy. Chindalore and co-workers[32] conducted a phase II clinical trial to evaluate the safety and efficacy of Oxytrex in 360 patients with moderate to severe chronic pain caused by osteoarthritis of the knee or hip. Four treatment conditions were examined: Placebo, oxycodone 4 times a day (qid), Oxytrex qid, and Oxytrex twice a day (bid). Results indicated that the Oxytrex bid group received a lower daily dose of naltrexone than the Oxytrex qid group and that the Oxytrex bid group produced a 39% reduction in pain intensity, which was significantly greater than that of the placebo, oxycodone qid, and Oxytrex qid groups. The Oxytrex bid group was also superior to the placebo group in quality of analgesia, duration of pain control each day, and patients' global assessments.

Additionally, the potential effects that ultra-low doses of naltrexone may reduce abuse or dependence liability (or decrease the reinforcing effects of opioids) were examined in human subjects. Tompkins and colleagues[33] conducted a double-blind, placebo-controlled study to investigate the subjective and physiologic effects of combining oral oxycodone and ultra-low naltrexone doses in 14 experienced opioid abusers. Seven acute drug conditions given at least 5 days apart were compared in a within-subject crossover design: placebo, oxycodone 20 mg, oxycodone 40 mg, plus each of the active oxycodone doses combined with 0.0001 and 0.001 mg naltrexone. Results showed no significant differences or evident trends associated with the addition of either naltrexone dose on any abuse liability indices. They thus suggest that the addition of ultra–low-dose naltrexone to oxycodone does not decrease abuse liability of acutely administered oxycodone in experienced opioid abusers.

Considered jointly, well-designed randomized trials of chronic pain patients co-treated with morphine plus low-dose naltrexone or other opioid receptor antagonists are required to elucidate the degree to which selective antagonists of excitatory opioid receptor functions can reliably attenuate opioid tolerance and dependence liability.[29]

## Behavioral Therapies With Naltrexone

Contingency management (CM) and significant other involvement were evaluated as strategies to enhance treatment retention, medication compliance, and outcome for naltrexone treatment of opioid dependence in a randomized trial of 127 opioid-dependent patients.[34] Results showed that CM was associated with significant improvements in treatment retention and reduction in opioid use compared with standard naltrexone treatment. Additionally, assignment to significant other involvement did not improve retention, compliance, or substance abuse outcomes compared with CM. Significant effects for the significant other involvement condition over CM on retention, compliance, and drug use outcomes were seen only for the subgroup who attended at least 1 family counseling session. The use of CM with XR-NTX would seem a likely combination to enhance outcomes. In an approach known as behavioral naltrexone therapy, voucher incentives have been integrated with the community reinforcement approach and involvement of significant others to support abstinence from opioids and improve adherence.[35]

Although the relevant literature remains sparse, studies to date suggest that XR-NTX is superior to the oral form in reducing drug use and retaining patients in treatment.[23] Similarly, although the injectable formulation, once successfully administered, does ensure medication adherence for the 30-day period, it is still “short term” considering the need for long-term treatment for most opioid-addicted patients. Research is clearly needed to evaluate compliance issues of long-acting depot naltrexone over an extended period of time and to determine whether behavioral therapies, such as CM, can be targeted to address compliance issues that may remain even with long-acting depot naltrexone.

## The Future of Extended-Release Depot Naltrexone Treatment for Addiction

### Depot Naltrexone for Other Indications

Alcohol dependence was the original indication for which FDA approval of XR-NTX (as Vivitrol) was obtained in April 2006. Opioid addiction was the logical next application of the medication, and the use of XR-NTX for other drug use disorders seems promising based on work that has examined naltrexone in oral form in research settings. For example, Swedish researchers have found positive results for naltrexone used in treating individuals dependent on amphetamine,[36] and subsequent research is seeking to confirm efficacy and safety in methamphetamine-dependent individuals.

Naltrexone could be effective for treatment of cocaine use disorder, cannabis use disorder, gambling disorder, eating disorder, and other behavioral conditions. Under-lying the presumed efficacy are mechanistic arguments based on the opioid system; naltrexone's ability to reduce the reinforcing effects of alcohol, opioids, and other drugs appears to derive from a blockade of effects of endogenous opioid peptides by occupation and binding of

opioid receptors. In a study of combination opioid and stimulant abusers, Comer and colleagues[3] found that cocaine use was reduced among the portion of the sample randomized to 384 mg of extended-release naltrexone.

Combining naltrexone with the partial agonist buprenorphine may reduce cocaine use; a multicenter trial is currently underway in an effort of the National Institute on Drug Abuse Clinical Trial Network, to examine buprenorphine for treatment of cocaine dependence in opioid-experienced individuals who are also receiving XR-NTX to blunt the reinforcing effects from the partial agonist action of buprenorphine. This is yet another example of the range of potential clinical applications of XR-NTX.

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**Key Points**

- The major problem with oral naltrexone is noncompliance. Administration of naltrexone as an intramuscular injection may be less onerous and improve compliance because it occurs only once a month (ie, extended-release depot naltrexone).
- To initiate treatment with extended-release depot naltrexone, steps should be taken to ensure that the patient is sufficiently free from physical dependence on opioids (eg, detoxification).
- Research on naltrexone in combination with other medications suggests many opportunities for studying mixed receptor activities in the treatment of opioid and other drug addictions.