

Pharmacological enhancement of naltrexone treatment for opioid dependence: a review

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Purpose: Opioid dependence (OD) is a serious and growing clinical condition with increasing social costs that requires expanding treatment beyond opioid agonist substitution. The opioid antagonist naltrexone has displayed a remarkable association of theoretical effectiveness and poor clinical utility in treating OD due to noncompliant behavior and low acceptability among patients, only partly modified by psychosocial interventions. We reviewed pharmacological studies, including naltrexone depot formulations and combination treatments.

Method: We searched PubMed for clinical studies on the use of naltrexone implants and slow-release injections in OD, and investigations using adjunct medications to improve naltrexone maintenance therapy of OD. We discussed the results in view of their application to the clinical practice.

Results: Significant reduction in opioid use and improved retention in treatment have been found in several studies using depot naltrexone formulations, some of which are controlled clinical trials. Pilot investigations have gathered initial positive results on the use of naltrexone in combination with serotonin reuptake inhibitors, α -2 adrenergic, opioid, and γ -aminobutyric acid agonist medications.

Conclusion: Current evidence suggests that more research on effectiveness and safety is needed in support of depot naltrexone treatment for OD. Further research comparing slow-release with oral naltrexone and opioid agonist medications will help characterize the role of opioid antagonist-mediated treatment of OD. Preliminary investigations on naltrexone combination treatments suggest the opportunity to continue study of new mixed receptor activities for the treatment of OD and other drug addictions.

Keywords: extended-release, naltrexone, implant, injection, depot, combination

Introduction

Illicit opioid use and opioid dependence (OD) are growing critical health issues requiring enhanced prevention and treatment efforts.^{1,2} Only a small proportion of OD individuals currently receive treatment,² and effective options are limited. Agonist maintenance therapy yields better outcomes, but has low availability.^{3,4} There is ambivalence toward this form of treatment in many patients and practitioners.⁵⁻⁷ There is also concern over the clinical correlates of long-term opioid agonist use in several organ systems and in the immune function.⁸⁻¹⁰ Among those who receive opioid agonist treatment, there is substantial attrition and many patients continue to abuse illicit drugs or alcohol,^{11,12} as if craving and appetitive behaviors were not consistently controlled.¹³ The opioid antagonist naltrexone is the only approved medication for OD that is not a controlled substance, nor does it display abuse potential. Thus, it offers a safe alternative for treatment expansion. Unfortunately, using naltrexone to treat OD

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patients has shown limited benefits, compared with the opioid agonist methadone and buprenorphine.^{14–16}

The validity of an antagonist therapy of OD was proposed by Wikler,¹⁷ and is based on the behavioral concept of “extinction.” The euphoric effects of opioids reinforce the self-administration behavior and are blocked when an individual is being treated with naltrexone. The continuous lack of reinforcement would gradually result in the extinction of such behavior. However, naltrexone has been successful only among highly motivated groups of OD, including impaired professionals, parolees, and probationers.^{18–21} Others emphasize the importance of close supervision for a successful naltrexone therapy approach, which would explain widely divergent outcomes.^{22,23} Studies have also shown that a comparatively low proportion of patients choose to start naltrexone treatment.²⁴ Among those who do, many drop out early: one quarter after a few days,²⁵ and as many as half in the first few weeks of treatment.²⁶

Along with other reasons for poor treatment retention and low patient compliance, there may be the lack of drug reinforcement when naltrexone is taken and the lack of negative consequences, including withdrawal symptoms, when it is discontinued. It has also been suggested that patients are reluctant to take naltrexone because of fear of symptoms, such as dysphoria or depression,^{27,28} despite the lack of evidence collected by reviews and clinical studies on naltrexone treatment for OD.^{29–31}

Behavioral therapy and contingency management have been investigated to alleviate naltrexone’s shortcomings. Study results have shown that reinforcement for naltrexone ingestion increases treatment retention and compliance with naltrexone therapy.^{32,33} However, recent investigations have underscored limits in the ability of behavioral therapy to help overcome poor adherence to oral naltrexone and suggest considering the use of formulations that do not include daily, or quasi-daily, administration of the medication.^{34–36}

The development of sustained-release or depot formulations of naltrexone has been a long-term goal to improve compliance. Pharmacological combination treatments have also received attention to increase naltrexone acceptability. In this paper, we review available evidence on these methods of enhancing naltrexone therapy of OD, as shown in peer-reviewed clinical investigations.

Clinical pharmacology of naltrexone

Naltrexone was developed in the early 1970s and its competitive opioid antagonism was tested in early studies with heroin and other opioids.^{37,38} Daily dosing of oral N-terminal

teloptide (NTX) results in fluctuating plasma concentrations of the drug.³⁹ A high first-pass metabolism causes the concentration of naltrexone and the active metabolite 6beta-naltrexol to peak within the first hour after oral dosing, followed by a steady decline each day during treatment.⁴⁰ Although the plasma half-life of naltrexone and 6beta-naltrexol is only 10–12 hours,⁴¹ studies using C11 carfentanil have shown that a single 50 mg dose blocks brain μ receptors for 48–72 hours,⁴² with plasma levels of 1–2 ng/mL that antagonize the euphoric effects of relevant intravenous doses of heroin.⁴³ This duration of action may be an advantage in that one or two missed doses would not leave the patient unprotected. However, clinical studies have shown that missing even a few doses of naltrexone could have negative consequences, leading to full relapse into opioid use and discontinuation of the treatment, despite intensive clinical interventions.³⁶ One explanation may be associated with a different naltrexone affinity at opioid receptors. Naltrexone has the highest affinity for μ receptors, and shows 10–25 times lower affinity for κ and δ receptors (Table 1). Activity at the three main opioid receptor subtypes indicates its ability to modulate dopaminergic, noradrenergic, and serotonergic transmission, influencing the motivational, stress-regulating, and mood-regulating systems.⁴⁴ This broad spectrum effect has also been suggested to help control the intake of other drugs and alcohol⁴⁵ and may be significantly reduced with less than daily administration of the medication. Of course the availability of depot preparations or the adjunct of other medications with ‘complementary’ action at opioid receptors (eg, buprenorphine, see Table 1) may add consistency to naltrexone’s effects.

Sustained-release naltrexone implants

Several types of naltrexone implants are available for insertion, usually in the subcutaneous tissue of the lower abdominal wall. More extensive published data exist on a few preparations. An implant containing 1 g of naltrexone compounded with magnesium stearate (Wedgewood Implant®, Wedgewood Pharmacy, Sewell, NJ) releases naltrexone at

Table 1 Naltrexone and buprenorphine: opioid receptor activity profiles

	Receptor binding Kior IC ₅₀			
	μ	κ	δ	ORL-1
Naltrexone	0.37	4.8	9.4	3,818 ^a
Buprenorphine	0.77	1.1	2.2	8.4 ^b

Notes: Unless otherwise noted, values are from Schmidt et al.⁴⁶

^aMcLeod et al;⁴⁷ ^bWnendt et al.⁴⁸

levels above 1 ng/mL during 30–60 days, associated with significant inter-individual variation.⁴⁹ Another type of implant containing 1 g of naltrexone (Prodeton[®], Fidelity Capital, Moscow, Russia) is approved for the treatment of OD in the Russian Federation. Available data suggest that it reaches naltrexone levels above 20 ng/mL, despite considerable inter-individual variation.⁵⁰ A third implant formulation consists of sets of 10, 20, or 30 pellets containing a polylactic-based polymer and naltrexone at doses of 1.1, 2.2, or 3.3 g (O'Neil Implant[®], Go Medical Industries, Perth, Australia). Naltrexone release is found to be 1–2 ng/mL, for 3 and 5 months, respectively with the 10-pellet and 20-pellet implants, and reaches 7 months with the 30-pellet ones.^{51,52}

Clinical studies

A significant body of uncontrolled studies suggests a superiority of naltrexone implants over oral naltrexone in maintaining OD individuals opiate-free, up to 12 months after initiating treatment and sometimes in large populations.^{23,53} Nonrandomized trials have tested the feasibility of the treatment,^{54,55} and quality of opioid blockade,⁵⁶ showing short- and long-term positive outcomes.^{57–61}

Three randomized clinical trials have compared implants to oral naltrexone, placebo, or treatment as usual. Two of them were randomized controlled trials (RCTs).

Hulse et al⁶² examined the safety and efficacy of the treatment among heroin-dependent individuals in a 6-month RCT. Seventy patients received 50 mg/day oral naltrexone plus placebo implants (n = 35) or a single-dose 2.3 g naltrexone implant plus placebo tablets (n = 35). Plasma naltrexone levels were found to be between 1 and 2 ng/mL for a longer time in the naltrexone implant group. Results showed that more patients receiving oral naltrexone had plasma naltrexone levels below 2 ng/mL in the first 2 months of treatment ($P = 0.001$ and 0.01 , respectively) and a higher proportion of them had resumed heroin use by the end of the study compared with the naltrexone implant group ($P = 0.003$). Time to relapse was shorter among oral naltrexone patients (115 days vs 158 days). One serious adverse event was associated with surgical implantation, and no major adverse events were recorded. Given the association of consistent plasma naltrexone levels with opioid abstinence, the authors suggested the effectiveness of the treatment to be associated with more effective μ -opioid receptor blockade. Secondary data analyses showed that effective treatment was achieved at naltrexone levels between 1 and 3 ng/mL and that implant treatment was associated with reduced craving and relapse.⁶³

In the study by Kunoe et al,⁶⁴ a group of 56 abstinence-oriented patients who completed inpatient treatment for OD were randomly and openly assigned to receive either a 6-month naltrexone implant or the usual no-naltrexone after-care, including counseling and vocational services. Patients receiving naltrexone had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period (both $P = 0.05$). Blood tests showed naltrexone levels above 1 ng/mL for the duration of the study. Two patients died, neither of whom had received an implant.

Krupitsky et al⁶⁵ examined three medication groups (n = 102 per group) in a 6-month RCT. Patients received naltrexone implant (1000 mg, implanted every other month), oral naltrexone (50 mg/day) or placebo. Available data include the results of an interim analysis on 190 patients. Opiate-positive urines at 6 months were lowest in the naltrexone implant group (63%) and higher in the oral naltrexone and placebo groups (87% and 86%, respectively). Retention was also significantly higher in the naltrexone implant group compared with the other groups ($P < 0.01$).

Injections

Injectable naltrexone preparations are administered intramuscularly in the gluteal region. Three different formulations, containing naltrexone-loaded microspheres of polymers of polylactide (Naltrel[®], DrugAbuse Sciences, Inc, Paris, France) or polylactide-co-glycolide (Vivitrol[®], Alkermes, Inc, Cambridge, MA; Depotrex[®], Biotek, Inc, Woburn, MA) have been clinically tested, with dosages ranging from 75 to 400 mg.^{40,66–68} The polylactide-co-glycolidepolymer formulation Vivitrol[®] containing 380 mg of naltrexone received United States Food and Drug Administration (FDA) approval for treatment of alcohol dependence in April 2006 and for relapse prevention in OD patients after detoxification treatment in October 2010.⁶⁹ This formulation releases naltrexone at levels above 1 ng/mL for about 4–5 weeks,⁷⁰ with no need to adjust the dosage to weight, age, gender, or health status.⁷¹

Clinical studies

Nonrandomized investigations have shown the ability of slow-release naltrexone injection to block opioid effects,^{72,73} and help maintain abstinence in different populations of OD patients, including adolescents.^{66,74}

Three randomized, clinical studies have compared injectable naltrexone with oral naltrexone or placebo.

Comer et al⁷⁵ studied the efficacy of extended-release injectable naltrexone for relapse prevention among heroin-dependent individuals in an RCT. Sixty patients were stratified

by sex and years of heroin use and randomized to receive placebo, 192 mg, or 384 mg of extended-release naltrexone intramuscular injections dosed on weeks 1 and 5. In addition to medication, patients received regular counseling. At the end of 2 months, 39%, 60%, and 68% of the placebo, 192 mg naltrexone, and 384 mg naltrexone groups, respectively, were still in treatment. Mean treatment dropout occurred in 27 days, 36 days, and 48 days for the placebo, 192 mg naltrexone, and 384 mg naltrexone groups, respectively. Assuming that missing urine samples were positive, patients receiving placebo had the lowest mean percentage of negative urine samples (25.3%), with the highest mean percentage of negative urine samples in the patient group receiving 384 mg of naltrexone (61.9%) and a significant main group effect ($P = 0.03$). Without that assumption, the treatment effect was no longer significant. Also, the number of patients retained in treatment did not show significant differences between groups. This lack of significance may have occurred because the study was not adequately powered, given the small sample size and three conditions of treatment.

Brooks et al⁷⁶ utilizing a quasi-experimental uncontrolled design compared early treatment retention and opiate use confirmed by urine in OD patients in two concurrent randomized clinical trials of oral ($n = 69$) and 192 mg or 384 mg extended-release injectable naltrexone ($n = 42$). Patients receiving injectable naltrexone had higher mean days retained in treatment ($P = 0.012$), and patients with more severe heroin use had better treatment retention with oral naltrexone and therapy than extended-release injectable naltrexone and therapy. The therapeutic modalities employed in the two studies were different, and the authors attributed the improved retention in the severe heroin use group to the intensive psychosocial treatments received in addition to oral naltrexone.

Krupitsky et al completed a multisite RCT, and the results were reported by Gastfriend.⁶⁹ In the study, monthly injections of extended-release naltrexone 380 mg ($n = 126$) or placebo ($n = 124$) were combined with 12 biweekly sessions of drug counseling. Overall, the median patient taking extended-release naltrexone had confirmed abstinence during 90% of study weeks 5–24, compared to 35% for placebo ($P = 0.0002$). With extended-release naltrexone, 36% of patients maintained complete abstinence for weeks 5–24 vs 23% of placebo patients ($P = 0.02$). Naltrexone-treated patients also had significantly more self-reported opioid-free days ($P = 0.0004$), less craving ($P = 0.0002$), less relapse to physiological dependence as documented by positive naloxone challenge ($P < 0.0001$), longer median retention

($P = 0.004$; 168 days vs 96 days for placebo), and significant benefits on health outcomes, such as reduced human immunodeficiency virus (HIV) drug-risk behavior. Transaminases were more frequently elevated with extended-release naltrexone than placebo, but were isolated and transient, and there was no evidence of hepatic injury. Serious adverse events most commonly consisted of infectious processes, including autoimmune deficiency syndrome/HIV, and were 2.4% among extended-release naltrexone patients and 3.2% among placebo patients. No overdose events, suicide attempts, or deaths were reported.

Clinical use of sustained-release naltrexone

Although there is significant preliminary evidence of efficacy, the use of sustained-release formulations in association with relapse prevention therapy needs further research in large controlled trials with oral naltrexone and opioid agonist treatment, to improve the understanding on the role of the antagonist treatment for OD. At this point, we have found results of retrospective studies in limited samples suggesting that sustained-release naltrexone can reduce drug use and drug-related hospitalizations as much as methadone treatment does,⁶⁰ or more.⁷⁷ Moreover, the mortality profile in samples of patients treated with naltrexone implant is comparable to that of buprenorphine or methadone, or to the normal population.^{23,78,79}

Side effects

Some common adverse effects such as nausea, vomiting, headache, fatigue, and muscle cramps show a degree of consistency between sustained-release formulations and oral naltrexone,^{80,81} and have been found to be mild to moderate.^{62,64,75} Although lower plasma concentrations and fewer peaks in the pharmacokinetic profile of naltrexone sustained-release formulations may justify a reduced intensity of adverse effects, direct comparisons of safety outcomes between implant or injection formulations and tablets are lacking. Local adverse effects such as pain, induration, infection, and allergic tissue reaction may occur when administering naltrexone injections or implants and were found to be more common among patients receiving naltrexone than placebo injections.^{75,82–84} Data on site-related adverse effects of naltrexone implants indicate a low rate of events, though they are scarce and mostly limited to single-group studies.^{52,85} Attempts at self-removal of naltrexone pellets can cause wounds, infections, and scarring and have not been ruled out in some cases.⁶⁴

Naltrexone in all forms carries a black-box warning for hepatotoxicity, and warnings for use in patients with elevated hepatic enzymes and acute hepatitis, deriving from clinical reports on the use of oral naltrexone. Hepatotoxicity has been historically observed in obese patients and at oral doses about five-fold over the recommended dose.⁸⁶ Reports indicate that an interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and >100 mg oral naltrexone may lead to hepatotoxicity in alcohol-dependent subjects.^{87,88} Clinicians should be careful in administering high doses of naltrexone especially in the presence of comorbid alcohol- and opioid-use disorders and should warn patients of such potentially dangerous drug interaction. In large trials of alcohol-dependent patients who were administered slow-release injectable naltrexone or placebo, the existence of high risk individuals among heavy drinkers, obese patients, and those taking NSAIDs was confirmed, though no increase in hepatic enzymes or hepatic-related adverse events was found with injectable naltrexone compared to placebo.^{84,89} Further studies in patients with alcohol-induced liver impairment failed to detect naltrexone injection-associated worsening of liver function.⁴⁰ In a case report of an OD patient presenting with acute hepatitis during treatment with a 1-g naltrexone implant, naltrexone did not affect the patient's recovery.⁹⁰

Limitations

Some characteristics of the treatment with sustained-release naltrexone may affect its widespread clinical use.

Administration and cost

Modalities of preserving and administering the slow-release naltrexone formulations require a 'set-up' and the coordinated effort of several physicians, including psychiatrist, internist, and anesthesiologist. In some countries, the cost of depot naltrexone may significantly surpass that of the oral formulation. For example, the cost per day of the FDA-approved extended-release naltrexone formulation is 10–15 times higher than that of the oral preparation. This could affect the choice of treatment, though cost-effective analysis may confirm significantly reduced health care expenses using depot naltrexone for OD, as already demonstrated in alcohol dependence.⁹¹

Naltrexone induction

The common methods of controlling withdrawal and safe transfer of OD patients to naltrexone are expensive and time consuming and may contribute to its reduced use.¹⁹ In accordance with oral naltrexone, OD patients are induced to

clinically-approved long-acting NTX formulations usually after inpatient detoxification and should remain opioid-free for a minimum of 7–10 days (Vivitrol[®] insert package). These measures aim at preventing the onset of intense withdrawal that could be difficult to treat because of the long-lasting effects of sustained-release naltrexone, though require conditions of treatment that are not easily accessible. In addition, having patients wait increases chances of vulnerability to drug use and drop out.⁹² Existing approaches using different sedation techniques or naltrexone titration methods to ease the transfer needs replication and/or wider availability.^{93–95} New safe methods to reduce time and discomfort of the transition are warranted.

Risk of overdose

The risk of death related to oral naltrexone appears higher than that associated with methadone treatment.⁹⁶ Deaths and overdoses have been reported during long-acting naltrexone treatment and following its discontinuation.^{59,97,98} A consistent and prolonged dosing exposure using sustained-release naltrexone may contribute to enhance the μ receptor sensitivity to opioids of an abstinent individual previously tolerant to larger doses of opiates. There are retrospective data showing no significant increase in overdose-related deaths with depot formulations,⁷⁹ but attempts of self-testing the competitive antagonist blockade have been reported.^{56,72} Therefore, longitudinal controlled studies are needed. Patients starting treatment with naltrexone need to be carefully advised of the risks of overdose with opiates during treatment with naltrexone, as well as after discontinuation.

Management of pain

Management of intense pain during treatment with sustained-release naltrexone requires a multidisciplinary team and may be not possible in an outpatient setting, as adequate analgesia would not be attainable with oral opioids. Patient cases are reported where nonopioid analgesics or a regional nerve blockade were used and provided effective analgesia.⁹⁹ If opioid therapy is required as part of anesthesia or analgesia, patients should be monitored in an anesthesia care setting by personnel trained in the use of anesthetic drugs and in the management of the respiratory effects of potent opioids, including the establishment and maintenance of a patent airway, assisted ventilation, and cardiopulmonary resuscitation.

Pharmacological combinations

The initial use of medications in combination with naltrexone to ease opioid withdrawal¹⁰⁰ has in some cases extended to supporting antagonist maintenance therapy and suggests

the opportunity to further study mixed receptor activities and their application to the treatment of OD and other addictions.

Naltrexone and serotonin reuptake inhibitors (SSRIs)

Landabaso et al¹⁰¹ administered fluoxetine to 112 detoxified heroin users newly admitted to naltrexone treatment and found that patients randomized to receive the medication showed a significantly higher retention rate in treatment at 6 and 12 months than controls. In a subsequent RCT of 280 OD patients,¹⁰² adding fluoxetine to naltrexone did not further improve the already significant increases in treatment retention and opioid abstinence after 6 months in patients treated with the opioid antagonist agent, compared with naltrexone placebo. However, the results were close to significance among women receiving naltrexone and fluoxetine compared with those receiving naltrexone and fluoxetine placebo. Fluoxetine alone was not superior to placebo for relapse prevention, although it was associated with twice as many patients who remained in treatment. In a study of 98 OD patients by Gerra et al,¹⁰³ the administration of fluoxetine with naltrexone was associated with reduced craving, hostility, and relapse in a subgroup of patients with high inward hostility, late onset of the disease, and preference for heroin and alcohol, as opposed to those with outward hostility, legal problems, and heroine-cocaine preference, or to control opioid abusers with no 'serotonergic system sensitivity'. Additionally, Farren and O'Malley¹⁰⁴ conducted an RCT of naltrexone in combination with sertraline in 13 OD patients. The combination therapy was associated with an initial increase of retention in treatment relative to naltrexone alone, but the effect diminished over 3 months.

Naltrexone and presynaptic α -adrenergic agonists

In an open-label, single-blind pilot study by Sinha et al,¹⁰⁵ 18 opioid-detoxified patients received naltrexone (50 mg) and lofexidine (2.4 mg) daily for 1 month. Patients were then continued on naltrexone for 4 more weeks and eight of them were kept on lofexidine, while 10 others received identical-looking pills containing lofexidine doses that were tapered off over several days. Of the 13 patients who completed the study, 80% of those who continued to receive combination therapy submitted opiate-free urine samples throughout the 4-week period, compared with 25% of those tapered to placebo. A follow-up laboratory session that exposed 10 patients to stressful and opiate-related stimuli showed that

lofexidine, but not placebo lofexidine, reduced the patients' reaction to stress, stress-induced opiate craving, and negative emotions, all of which are associated with relapse. Presently, an ongoing large (n = 300) RCT is studying the combination of naltrexone and guanfacine (another presynaptic α -2 adrenergic agonist). An interim analysis of half of the sample has not found a significant additive effect of guanfacine on preventing relapse.⁶⁵

Naltrexone and opioid agonists

The combined administration of buprenorphine 4 mg sublingual and naltrexone 50 mg oral following opioid detoxification has been tested in two clinical investigations. In a nonrandomized 3-month observational study,¹⁰⁶ Gerra et al showed that retention rates in 30 patients receiving naltrexone and 30 receiving naltrexone + buprenorphine at 3 months were 40% (12 patients) and 73.33% (22 patients), respectively. Patients treated with naltrexone in combination with buprenorphine showed a significantly lower rate of positive urines for opioids (4.45%) and cocaine metabolites (9.09%) than those treated with naltrexone alone (25% opioids; 33.33% cocaine). Behavioral and psychological symptoms, such as craving, irritability, and depression, were also improved in the buprenorphine/naltrexone group. The same combination of medications was previously investigated by Rothman et al¹⁰⁷ in 15 OD subjects following detoxification. Although the absence of a "naltrexone only" group precluded any firm conclusion, abstinence and retention rates were not dissimilar to those described by Gerra et al.

Naltrexone and γ -aminobutyric acid (GABA) agonists

Stella et al¹⁰⁸ evaluated whether NTX combined with the benzodiazepine prazepam was more effective than NTX in preventing relapse in a 6-month study. Fifty-six OD subjects were randomized to receive naltrexone and prazepam (10 mg twice a day) or placebo with psychosocial treatment, naltrexone with psychosocial treatment, and psychosocial treatment alone. All groups underwent drug urine tests twice weekly. By the end of the study, a significant higher number of patients receiving naltrexone in combination with prazepam had remained opioid-free (85.7%) compared with those receiving naltrexone and placebo or naltrexone alone (both 42.9%), or counseling only (21.4%). Additionally, more patients receiving the combination treatment were cannabis-free. The authors suggested that the addition of a GABA agonist medication (eg, prazepam) may significantly improve relapse prevention during naltrexone treatment of OD patients.

Rationale on the clinical use of combination treatments

Small pilot studies suggest the feasibility to further explore the effects of the addition of various medications to naltrexone. Considerations on the pharmacological rationale for each medication group follow.

Antidepressants

The use of antidepressants in combination with opioid agonist medications is relatively common in clinical practice, but has not been found to effectively reduce drug abuse or favor retention in treatment among depressed patients.¹⁰⁹ SSRIs or other antidepressants may help manage stress in nondepressed OD individuals and address depressive symptoms, irritability, and dysphoria commonly associated with craving and relapse during naltrexone induction and early stabilization.¹¹⁰

α -2 agonists

Increased stress levels and stress-induced opioid cravings following discontinuation of opioid agonist medications is not consistently controlled during naltrexone therapy.^{111,112} α -2 adrenergic agonist medications that have been administered to reduce hyperadrenergic activity during opioid withdrawal, such as clonidine, lofexidine, and guanfacine, also display discriminative stimulus effects and reinforcing properties in animals,^{113,114} and may be used to improve long-term naltrexone outcomes, if the associated orthostatic hypotension can be controlled.

Opioid agonists

Alcohol and nonopioid drug use as well as associated morbidity are significant unresolved problems in naltrexone maintenance treatment.⁷⁷ Rothman and co-workers¹⁰⁷ first proposed the combination naltrexone/buprenorphine as a functional κ -opioid receptor antagonist to help overcome dysphoric symptoms associated with prolonged opioid withdrawal discomfort and cocaine use. Buprenorphine shows strong κ - and δ -opioid receptor affinity that reinforces naltrexone's weak antagonist action, associated with unique significant agonism at the nociceptin receptor (ORL-1) (Table 1). The mixed receptor activity of this combination justifies its effects not only on dysphoric mood and opioid-seeking behavior and use, but also on cocaine and alcohol abuse.¹¹⁵ Other opioid agonist/antagonist combinations, using extremely low dose naltrexone with methadone, have shown the potential to reduce opioid withdrawal and physical dependence,¹¹⁶ which may help in the early induction phase to naltrexone maintenance.

GABA agonists

GABA-glutamate imbalance is thought to play a role in the development and expression of sleeping disorders, anxiety, and drug abuse/withdrawal.^{117–119} Insomnia and anxiety are common symptoms in naltrexone-treated OD patients³¹ and have been noted to last through naltrexone induction and stabilization.¹²⁰ The use of a medication resulting in net GABA agonism and lacking the abuse liability displayed by benzodiazepines may help control specific behavioral problems associated with anxiety and insomnia during naltrexone treatment. One example is the ongoing experimentation with the N-methyl-D-aspartate-glutamate receptor antagonist memantine in addition to naltrexone injection in OD patients (ClinicalTrials.gov identifier NCT00476242). GABA receptor agonists, such as baclofen, vigabatrin, tiagabine, and gabapentin, have shown potential utility as adjunct treatments for OD and withdrawal,^{121–125} though no data on their use with naltrexone are available.

Other drug mechanisms that contribute to reduced opioid withdrawal severity and may produce a complementary or synergistic effect with opioid antagonists remain untested in OD. For example, corticotropin-releasing factor type 1 receptor antagonists appear to regulate stress-induced drug taking behavior that can be paired to the basal control exerted by naltrexone in alcohol-dependent animals,¹²⁶ whereas the glutamate partial agonist D-cycloserine has shown conditioned opioid stimuli extinction characteristics in animals,¹²⁷ which may reinforce the extinction properties of naltrexone treatment.

Safety data on pharmacological combinations using naltrexone in OD individuals are limited. Although the studies we have reviewed for this paper did not report significant adverse events, available information from other sources is scarce.^{128,129}

Finally, a better characterization of individual phenotypes, perhaps using a pharmacogenetic approach, may help recognize subgroups of patients who can benefit from mixed pharmacological actions. One example is offered by the ongoing efforts to identify biological endophenotypes for naltrexone and acamprosate in the management of alcohol dependence that may lead to preselect potential responders to their combination.^{130,131}

Conclusion

Several studies, including RCTs, suggest that the use of naltrexone depot formulations in OD patients leads to significant reductions in opioid use and improved treatment retention. The consistent evidence from uncontrolled investigations

can serve as a path-finding experience. More importantly, larger, multicenter RCTs to measure the effectiveness of the treatment and trials comparing slow-release naltrexone with naltrexone tablets or agonist maintenance treatment are needed to confirm the initial findings and provide prospective data on patient safety and tolerability, characterizing the role of opioid antagonist treatment in OD. Previous experiences using long-acting formulations in the treatment of other psychiatric conditions such as schizophrenia have shown that this method can improve effectiveness of,¹³² acceptance of, and adherence to treatment,¹³³ significantly reducing the burden of disease.¹³⁴ Pilot studies combining naltrexone with other medications also suggest possible mechanisms that warrant further research to improve outcomes of OD treatment. Available techniques, such as pharmacogenetics, can help identify specific endophenotypes and find a better treatment match for patients. In conclusion, improving naltrexone outcome would expand the therapeutic options for OD and offer continuity of care to those patients who cannot access or choose not to initiate opioid agonist substitution therapy, and to many others when they discontinue methadone or buprenorphine treatment.

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