

25 - 29.25 Opioid Receptor Antagonists Naltrexone,

29.25 Opioid Receptor Antagonists: Naltrexone, Nalmefene, and Naloxone

Strain EC, Moody DE, Stoller KB, Walsh SL, Bigelow GE. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend.* 2004;74:37. Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194). Rockville, MD: Department of Health and Human Services; 2006. Tetrault JM, Kozal MJ, Chiarella J, Sullivan LE, Dinh AT, Fiellin DA. Association between risk behaviors and antiretroviral resistance in HIV-infected patients receiving opioid agonist treatment. *J Addict Med.* 2013;7(2):102-107.

29.25 Opioid Receptor Antagonists: Naltrexone, Nalmefene, and Naloxone

Naltrexone (Revia, Depade) and naloxone (Narcan) are competitive opioid antagonists. They bind to opioid receptors without causing their activation. Because these drugs induce opioid withdrawal effects in people using full opioid agonists, these drugs are classified as opioid antagonists. Naltrexone is the most widely used of these drugs. It has a relatively long half-life, is orally effective, is not associated with dysphoria, and is administered once daily. Naloxone, which predated naltrexone to treat narcotic overdose, became less widely used for preventing relapse to opiate use in detoxified opiate addicts. Since its introduction, naltrexone has been tried for the treatment of a wide range of psychiatric disorders, including, among others, eating disorders, autism, self-injurious behavior, cocaine dependence, gambling, and alcoholism. Naltrexone was approved for the treatment of alcohol dependence in 1994. A number of generic formulations are also available. An extended-release, once-a-month injectable suspension (Vivitrol) was also approved in 2006. Nalmefene (Revex) is indicated for the complete or partial reversal of opioid drug effects and in the management of known or suspected opioid overdose. An oral formulation of nalmefene is available in some countries but not in the United States. Nalmefene (Revex) is an opioid receptor antagonist that is sometimes used in the management of alcohol dependence.

PHARMACOLOGICAL ACTIONS Oral opioid receptor antagonists are rapidly absorbed from the

gastrointestinal (GI) tract, but because of first-pass hepatic metabolism, only 60 percent of a dose of naltrexone and 40 to 50 percent of a dose of nalmefene reach the systemic circulation unchanged. Peak concentrations of naltrexone and its active metabolite, 6- β -naltrexol, are achieved within 1 hour of ingestion. The half-life of naltrexone is 1 to 3 hours and the half-life of 6- β -naltrexol is 13 hours. Peak concentrations of nalmefene are achieved in about 1 to 2 hours, and the half-life is 8 to 10 hours. Clinically, a single dose of naltrexone effectively blocks the rewarding effects of opioids for 72 hours. Traces of 6- β -naltrexol may linger for up to 125 hours after a single dose. Naltrexone and nalmefene are competitive antagonists of opioid receptors. Understanding the pharmacology of opioid receptors can explain the difference in

adverse effects caused by naltrexone and nalmefene. Opioid receptors in the body are typed pharmacologically as μ , κ , or δ . Whereas activation of the κ - and δ -receptors is thought to reinforce opioid and alcohol consumption centrally, activation of μ -receptors is more closely associated with central and peripheral antiemetic effects. Because naltrexone is a relatively weak antagonist of κ - and δ -receptors and a potent μ -receptor antagonist, dosages of naltrexone that effectively reduce opioid and alcohol consumption also strongly block μ -receptors and therefore may cause nausea. Nalmefene, in contrast, is an equally potent antagonist of all three opioid receptor types, and dosages of nalmefene that effectively reduce opioid and alcohol consumption have no particularly increased effect on μ -receptors. Thus, nalmefene is associated clinically with few GI adverse effects. Naloxone has the highest affinity for the μ -receptor but is a competitive antagonist at the μ -, κ -, and δ -receptors. Whereas the effects of opioid receptor antagonists on opioid use are easily understood in terms of competitive inhibition of opioid receptors, the effects of opioid receptor antagonists on alcohol dependence are less straightforward and probably relate to the fact that the desire for and the effects of alcohol consumption appear to be regulated by several neurotransmitter systems, both opioid and nonopioid.

THERAPEUTIC INDICATIONS The combination of a cognitive-behavioral program plus use of opioid receptor antagonists is more successful than either the cognitive-behavioral program or use of opioid receptor antagonists alone. Naltrexone is used as a screening test to ensure that the patient is opioid-free before the induction of therapy with naltrexone (see “Naloxone Challenge Test” in Table 29.25-1). Table 29.25-1 Naloxone (Narcan) Challenge Test

Opioid Dependence Patients in detoxification programs are usually weaned from potent opioid agonists such as heroin over a period of days to weeks, during which emergent adrenergic withdrawal effects are treated as needed with clonidine (Catapres). A serial protocol is sometimes used in which potent agonists are gradually replaced by weaker agonists followed by mixed agonist-antagonists and then finally by pure antagonists. For example, an abuser of the potent agonist heroin would switch first to the weaker agonist methadone (Dolophine), then to the partial agonist buprenorphine (Buprenex) or levomethadyl acetate (ORLAAM)—commonly called LAAM—and finally, after a 7- to 10-day washout period, to a pure antagonist, such as naltrexone or nalmefene. However, even with gradual detoxification, some persons continue to experience mild adverse effects or opioid withdrawal symptoms for the first several weeks of treatment with naltrexone. As the opioid receptor agonist potency diminishes, so do the adverse consequences of discontinuing the drug. Thus, because there are no pharmacological barriers to discontinuation of pure opioid receptor antagonists, the social environment and frequent cognitive-behavioral intervention become extremely important factors supporting continued opioid abstinence. Because of poorly tolerated adverse symptoms, most persons not simultaneously enrolled in a cognitive-

behavioral program stop taking opioid receptor antagonists within 3 months. Compliance with the administration of an

opioid receptor antagonist regimen can also be increased with participation in a wellconceived voucher program. Issues of medication compliance should be a central focus of treatment. If a person with a history of opioid addiction stops taking a pure opioid receptor antagonist, the person's risk of relapse into opioid abuse is exceedingly high because reintroduction of a potent opioid agonist would yield a very rewarding subjective "high." In contrast, compliant persons do not develop tolerance to the therapeutic benefits of naltrexone even if it is administered continuously for 1 year or longer. Individuals may undergo several relapses and remissions before achieving long-term abstinence. Persons taking opioid receptor antagonists should also be warned that sufficiently high dosages of opioid agonists can overcome the receptor antagonism of naltrexone or nalmefene, which may lead to hazardous and unpredictable levels of receptor activation (see "Precautions and Adverse Reactions").

Rapid Detoxification To avoid the 7- to 10-day period of opioid abstinence generally recommended before use of opioid receptor antagonists, rapid detoxification protocols have been developed. Continuous administration of adjunct clonidine—to reduce the adrenergic withdrawal symptoms—and adjunct benzodiazepines, such as oxazepam (Serax)—to reduce muscle spasms and insomnia—can permit use of oral opioid receptor antagonists on the first day of opioid cessation. Detoxification can thus be completed within 48 to 72 hours, at which point opioid receptor antagonist maintenance is initiated. Moderately severe withdrawal symptoms may be experienced on the first day, but they taper off rapidly thereafter. Because of the potential hypotensive effects of clonidine, the blood pressure (BP) of persons undergoing rapid detoxification must be closely monitored for the first 8 hours. Outpatient rapid detoxification settings must therefore be adequately prepared to administer emergency care. The main advantage of rapid detoxification is that the transition from opioid abuse to maintenance treatment occurs over just 2 or 3 days. The completion of detoxification in as little time as possible minimizes the risk that the person will relapse into opioid abuse during the detoxification protocol.

Alcohol Dependence Opioid receptor antagonists are also used as adjuncts to cognitive-behavioral programs for treatment of alcohol dependence. Opioid receptor antagonists reduce alcohol craving and alcohol consumption, and they ameliorate the severity of relapses. The risk of relapse into heavy consumption of alcohol attributable to an effective cognitivebehavioral program alone may be halved with concomitant use of opioid receptor antagonists. The newer agent nalmefene has a number of potential pharmacological and clinical advantages over its predecessor naltrexone for treatment of alcohol dependence.

Whereas naltrexone may cause reversible transaminase elevations in persons who take dosages of 300 mg a day (which is six times the recommended dosage for treatment of alcohol and opioid dependence [50 mg a day]), nalmefene has not been associated with any hepatotoxicity. Clinically effective dosages of naltrexone are discontinued by 10 to 15 percent of persons because of adverse effects, most commonly nausea. In contrast, discontinuation of nalmefene because of an adverse event is rare at the clinically effective dosage of 20 mg a day and in the range of 10 percent at excessive dosages— that is, 80 mg a day. Because of its pharmacokinetic profile, a given dosage of nalmefene may also produce a more sustained opioid antagonist effect than does naltrexone. The efficacy of opioid receptor antagonists in reducing alcohol craving may be augmented with a selective serotonin reuptake inhibitor, although data from large trials are needed to assess this potential synergistic effect more fully.

PRECAUTIONS AND ADVERSE REACTIONS

Because opioid receptor antagonists are used to maintain a drug-free state after opioid detoxification, great care must be taken to ensure that an adequate washout period elapses—at least 5 days for a short-acting opioid such as heroin and at least 10 days for longer-acting opioids such as methadone—after the last dose of opioids and before the first dose of an opioid receptor antagonist is taken. The opioid-free state should be determined by self-report and urine toxicology screens. If any question persists of whether opioids are in the body despite a negative urine screen result, then a naloxone challenge test should be performed. Naloxone challenge is used because its opioid antagonism lasts less than 1 hour, but those of naltrexone and nalmefene may persist for more than 24 hours. Thus, any withdrawal effects elicited by naloxone will be relatively short lived (see “Dosage and Clinical Guidelines”). Symptoms of acute opioid withdrawal include drug craving, feeling of temperature change, musculoskeletal pain, and GI distress. Signs of opioid withdrawal include confusion, drowsiness, vomiting, and diarrhea. Naltrexone and nalmefene should not be taken if naloxone infusion causes any signs of opioid withdrawal except as part of a supervised rapid detoxification protocol. A set of adverse effects resembling a vestigial withdrawal syndrome tends to affect up to 10 percent of persons who take opioid receptor antagonists. Up to 15 percent of persons taking naltrexone may experience abdominal pain, cramps, nausea, and vomiting, which may be limited by transiently halving the dosage or altering the time of administration. Adverse central nervous system effects of naltrexone, experienced by up to 10 percent of persons, include headache, low energy, insomnia, anxiety, and nervousness. Joint and muscle pains may occur in up to 10 percent of persons taking naltrexone, as may rash. Naltrexone may cause dosage-related hepatic toxicity at dosages well in excess of 50 mg a day; 20 percent of persons taking 300 mg a day of naltrexone may experience serum aminotransferase concentrations 3 to 19 times the upper limit of normal. The hepatocellular injury of naltrexone appears to be a dose-related toxic effect rather than

an idiosyncratic reaction. At the lowest dosages of naltrexone required for effective opioid antagonism, hepatocellular injury is not typically observed. However, naltrexone dosages as low as 50 mg a day may be hepatotoxic in persons with underlying liver disease, such as persons with cirrhosis of the liver caused by chronic alcohol abuse. Serum aminotransferase concentrations should be monitored monthly for the first 6 months of naltrexone therapy and thereafter on the basis of clinical suspicion. Hepatic enzyme concentrations usually return to normal after discontinuation of naltrexone therapy. If analgesia is required while a dose of an opioid receptor antagonist is pharmacologically active, opioid agonists should be avoided in favor of benzodiazepines or other nonopioid analgesics. Persons taking opioid receptor antagonists should be instructed that low dosages of opioids will have no effect but larger dosages could overcome the receptor blockade and suddenly produce symptoms of profound opioid overdose, with sedation possibly progressing to coma or death. Use of opioid receptor antagonists is contraindicated in persons who are taking opioid agonists, small amounts of which may be present in over-the-counter antiemetic and antitussive preparations; in persons with acute hepatitis or hepatic failure; and in persons who are hypersensitive to the drugs. Because naltrexone is transported across the placenta, opioid receptor antagonists should only be taken by pregnant women if a compelling need outweighs the potential risks to the fetus. It is not known whether opioid receptor antagonists are distributed into breast milk. Opioid receptor antagonists are relatively safe drugs, and ingestion of high doses of opioid receptor antagonists should be treated with supportive measures combined with efforts to decrease GI absorption. Because buprenorphine has a high affinity and slow displacement from the opioid receptors, nalmefene may not completely reverse buprenorphine-

induced respiratory depression. **DRUG INTERACTIONS** Many drug interactions involving opioid receptor antagonists have been discussed earlier, including those with opioid agonists associated with drug abuse as well as those involving antiemetics and antitussives. Because of its extensive hepatic metabolism, naltrexone may affect or be affected by other drugs that influence hepatic enzyme levels. However, the clinical importance of these potential interactions is not known. One potentially hepatotoxic drug that has been used in some cases with opioid receptor antagonists is disulfiram (Antabuse). Although no adverse effects were observed, frequent laboratory monitoring is indicated when such combination therapy is contemplated. Opioid receptor antagonists have been reported to potentiate the sedation associated with use of thioridazine (Mellaril), an interaction that probably applies equally to all low-potency dopamine receptor antagonists. Intravenous nalmeferene has been administered after benzodiazepines, inhalational

anesthetics, muscle relaxants, and muscle relaxant antagonists administered in conjunction with general anesthetics without any adverse reactions. Care should be taken when using flumazenil (Romazicon) and nalmeferene together because both of these agents have been shown to induce seizures in preclinical studies. **LABORATORY INTERFERENCES** The potential for a false-positive urine for opiates using less specific urine screens such as enzyme-multiplied immunoassay technique (EMIT) may exist, given that naltrexone and nalmeferene are derivatives of oxymorphone. Thin-layer, gas-liquid, and highpressure liquid chromatographic methods used for the detection of opiates in the urine are not interfered with by naltrexone. **DOSAGE AND CLINICAL GUIDELINES** To avoid the possibility of precipitating an acute opioid withdrawal syndrome, several steps should be taken to ensure that the person is opioid free. Within a supervised detoxification setting, at least 5 days should elapse after the last dose of short-acting opioids, such as heroin, hydromorphone (Dilaudid), meperidine (Demerol), or morphine, and at least 10 days should elapse after the last dose of longer-acting opioids, such as methadone, before opioid antagonists are initiated. Briefer periods off opioids have been used in rapid detoxification protocols. To confirm that opioid detoxification is complete, urine toxicological screens should demonstrate no opioid metabolites. However, an individual may have a negative urine opioid screen result, yet still be physically dependent on opioids and thus susceptible to antagonist-induced withdrawal effects. Therefore, after the urine screen result is negative, a naloxone challenge test is recommended unless an adequate period of opioid abstinence can be reliably confirmed by observers (Table 29.25-1). The initial dosage of naltrexone for treatment of opioid or alcohol dependence is 50 mg a day, which should be achieved through gradual introduction, even when the naloxone challenge test result is negative. Various authorities begin with 5, 10, 12.5, or 25 mg and titrate up to the 50-mg dosage over a period ranging from 1 hour to 2 weeks while constantly monitoring for evidence of opioid withdrawal. When a daily dose of 50 mg is well tolerated, it may be averaged over a week by giving 100 mg on alternate days or 150 mg every third day. Such schedules may increase compliance. The corresponding therapeutic dosage of nalmeferene is 20 mg a day divided into two equal doses. Gradual titration of nalmeferene to this daily dose is probably a wise strategy, although clinical data on dosage strategies for nalmeferene are not yet available. To maximize compliance, it is recommended that family members directly observe ingestion of each dose. Random urine tests for opioid receptor antagonists and their metabolites as well as for ethanol or opioid metabolites should also be taken. Opioid receptor antagonists should be continued until the person is no longer considered psychologically at risk for relapse into opioid or alcohol abuse. This generally requires at least 6 months but may take longer, particularly if there are external stresses.

Nalmefene is available as a sterile solution for intravenous, intramuscular, and subcutaneous administration in two concentrations, containing 100 µg or 1.0 mg of nalmefene free base per milliliter. The 100 µg/mL concentration contains 110.8 µg of nalmefene hydrochloride and the 1.0 mg/mL concentration contains 1.108 mg of nalmefene hydrochloride per milliliter. Both concentrations contain 9.0 mg of sodium chloride per milliliter and the pH is adjusted to 3.9 with hydrochloric acid. Pharmacodynamic studies have shown that nalmefene has a longer duration of action than naloxone at fully reversing opiate activity. Rapid Detoxification Rapid detoxification has been standardized using naltrexone, although nalmefene would be expected to be equally effective with fewer adverse effects. In rapid detoxification protocols, the addicted person stops opioid use abruptly and begins the first opioid-free day by taking clonidine, 0.2 mg, orally every 2 hours for nine doses, to a maximum dose of 1.8 mg, during which time the BP is monitored every 30 to 60 minutes for the first 8 hours. Naltrexone, 12.5 mg, is administered 1 to 3 hours after the first dose of clonidine. To reduce muscle cramps and later insomnia, a short-acting benzodiazepine, such as oxazepam, 30 to 60 mg, is administered simultaneously with the first dose of clonidine, and half of the initial dose is readministered every 4 to 6 hours as needed. The maximum daily dosage of oxazepam should not exceed 180 mg. The person undergoing rapid detoxification should be accompanied home by a reliable escort. On the second day, similar doses of clonidine and the benzodiazepine are administered but with a single dose of naltrexone, 25 mg, taken in the morning. Relatively asymptomatic persons may return home after 3 to 4 hours. Administration of the daily maintenance dose of 50 mg of naltrexone is begun on the third day, and the dosages of clonidine and the benzodiazepine are gradually tapered off over 5 to 10 days. REFERENCES Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D. Combined pharmacotherapies and behavioral interventions for alcohol dependence—The COMBINE study: A randomized controlled trial. JAMA. 2006;295(17):2003. Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan D. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. Arch Gen Psychiatry. 2001;58:755. Grant JE, Kim SW. An open-label study of naltrexone in the treatment of kleptomania. J Clin Psychiatry. 2002;63(4):349. Grant JE, Kim SW, Potenza MN. Advances in the pharmacological treatment of pathological gambling. J Gambling Stud. 2003;19:85. Gueorguieva R, Wu R, Pittman B, O'Malley S, Krystal JH. New insights into the efficacy of naltrexone for alcohol dependence from the trajectory-based analyses. Biol Psychiatry. 2007;61(11):1290. Helm SI, Trescot AM, Colson J, Sehgal N, Silverman S. Opioid antagonists, partial agonists, and agonists/antagonists: The role of office-based detoxification. Pain Physician 2008;11:225. Johnson BA, Ait-Daoud N, Prihoda TJ. Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: From hypotheses to preliminary clinical evidence. Alcoholism Clin Exp Res. 2000;24(5):737.

Revision #1

Created 2026-01-04 19:51:49 UTC by Omar Ayman

Updated 2026-01-04 19:51:49 UTC by Omar Ayman