

# 24 - 29.24 Opioid Receptor Agonists

## 29.24 Opioid Receptor Agonists

randomized double-blind placebo-controlled trial. *Addiction*. 2005;100(4):489. Sasada K, Iwamoto K, Kawano N, et al. Effects of repeated dosing with mirtazapine, trazodone, or placebo on driving performance and cognitive function in healthy volunteers. *Human Psychopharmacology: Clinical and Experimental*. 2013;28(3):281-286. Schatzberg AF, Rush AJ, Arnow BA, Banks PL, Blalock JA. Chronic depression: Medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch Gen Psychiatry*. 2005;62(5):513. Schatzberg AF, Prather MR, Keller MB, Rush AJ, Laird LK. Clinical use of nefazodone in major depression: A 6-year perspective. *J Clin Psychiatry*. 2002;63(1):18. Tanimukai H, Murai T, Okazaki N, et al. An observational study of insomnia and nightmare treated with trazodone in patients with advanced cancer. *Am J Hosp Palliat Care*. 2013;30(4):359-362. Van Ameringen M, Mancini C, Oakman J. Nefazodone in the treatment of generalized social phobia: A randomized, placebo-controlled trial. *J Clin Psychiatry*. 2007;68(2):288. Xu JJ, Henstock PV, Dunn MC, Smith AR, Chabot JR, de Graaf D. Cellular imaging predictions of clinical drug-induced liver injury. *Toxicol Sci*. 2008;105(1):97.

### 29.24 Opioid Receptor Agonists

Opioid receptor agonists are a structurally diverse group of compounds that are used for pain management. These drugs are also called narcotics. Although highly effective as analgesics, they often cause dependence and are frequently diverted for recreational use. Commonly used opioid agonists for pain relief include morphine, hydromorphone (Dilaudid), codeine, meperidine (Demerol), oxycodone (OxyContin), buprenorphine (Buprenex), hydrocodone (Robidone), tramadol (Ultram), and fentanyl (Durogesic). Heroin is used as a street drug. Methadone is used both for pain management and for treatment of opiate addiction. This chapter focuses on the  $\mu$ -opioid receptor agonists that are most likely to be used in the treatment of psychiatric disorders instead of pain management. It is now recognized that the pharmacology of the opioid system is complex. There are multiple types of opioid receptors, with  $\mu$ - and  $\kappa$ -opioid receptors representing functionally opposing endogenous systems (Table 29.24-1). All of the compounds above, which represent the most extensively used narcotic analgesics, are agonists at  $\mu$ -opioid receptors. However, analgesic effects also result from antagonist effects on the  $\kappa$ -opioid receptor. Buprenorphine has mixed receptor effects, being primarily a  $\mu$ -opioid receptor agonist as well as a  $\kappa$ -opioid antagonist. Table 29.24-1  $\mu$ - and  $\kappa$ -Opiate Receptors

There is growing interest in the use of some drugs that act on opioid receptors as alternative treatments for a subpopulation of patients with refractory depression, as well as treatment for cutting behavior in patients with borderline personality disorder. Consideration of such off-label use is tempered by the well-known fact that ongoing, regular use of opioids produces dependence and tolerance and may lead to maladaptive use, functional impairment, and withdrawal symptoms. The prevalence of opioid use, abuse, and dependence, particularly in regard to prescription opioids, has risen in recent years. Before using opioid receptor agonists with patients who have failed on multiple conventional therapeutic agents, screen carefully for history of drug abuse, document the rationale for off-label use, establish treatment ground rules, obtain written consent, consult with primary care physician, and monitor closely. Avoid replacing "lost" prescriptions and providing early prescription renewals.

**PHARMACOLOGIC ACTIONS** Methadone and buprenorphine are absorbed rapidly from the GI tract. Hepatic first-pass metabolism significantly affects the bioavailability of each of the drugs but in markedly different ways. For methadone, hepatic enzymes reduce the bioavailability of an oral dosage by about half, an effect that is easily managed with dosage adjustments. For buprenorphine, first-pass intestinal and hepatic metabolism eliminates oral bioavailability almost completely. When used in opioid detoxification, buprenorphine is given sublingually in either a liquid or a tablet formulation. The peak plasma concentrations of oral methadone are reached within 2 to 6 hours, and the plasma half-life initially is 4 to 6 hours in opioid-naive persons and 24 to 36 hours after steady dosing of any type of opioid. Methadone is highly protein bound and equilibrates widely throughout the body, which ensures little postdosage variation in steady-state plasma concentrations. Elimination of a sublingual dosage of buprenorphine occurs in two phases: an initial phase with a half-life of 3 to 5 hours and a terminal phase with a half-life of more than 24 hours. Buprenorphine dissociates from its receptor binding site slowly, which permits an every-other-day dosing schedule. Methadone acts as pure agonists at  $\mu$ -opioid receptors and has negligible agonist or antagonist activity at  $\kappa$ - or  $\delta$ -opioid receptors. Buprenorphine is a partial agonist at  $\mu$ receptors, a potent antagonist at  $\kappa$ -receptors, and neither an agonist nor an antagonist at  $\delta$ -receptors.

**THERAPEUTIC INDICATIONS** Methadone Methadone is used for short-term detoxification (7 to 30 days), long-term detoxification (up to 180 days), and maintenance (treatment beyond 180 days) of opioid-dependent individuals. For these purposes, it is only available through designated clinics called methadone maintenance treatment programs (MMTPs) and in hospitals and prisons. Methadone is a schedule II drug, which means that its administration is tightly governed by specific federal laws and regulations. Enrollment in a methadone program reduces the risk of death by 70 percent; reduces illicit use of opioids and other substances of abuse; reduces criminal activity; reduces the risk of infectious diseases of all types, most importantly HIV and hepatitis B and C infection; and in pregnant women, reduces the risk of fetal and neonatal morbidity and mortality. The use of methadone maintenance frequently requires lifelong treatment. Some opioid-dependence treatment programs use a stepwise detoxification protocol in which a person addicted to heroin switches first to the strong agonist methadone; then to the weaker agonist buprenorphine; and finally to maintenance on an opioid receptor antagonist, such as naltrexone (ReVia). This approach minimizes the appearance of opioid withdrawal effects, which, if they occur, are mitigated with clonidine (Catapres). However, compliance with opioid receptor antagonist treatment is poor outside of settings using intensive cognitive-behavioral techniques. In contrast, noncompliance with methadone maintenance precipitates opioid withdrawal symptoms, which serve to reinforce the use of methadone and make cognitive-behavioral therapy less than

essential. Thus, some well-motivated, socially integrated former heroin addicts are able to use methadone for years without participation in a psychosocial support program. Data pooled from many reports indicate that methadone is more effective when taken at dosages in excess of 60 mg a day. The analgesic effects of methadone are sometimes used in the management of chronic pain when less addictive agents are ineffective. Pregnancy. Methadone maintenance, combined with effective psychosocial services and regular obstetric monitoring, significantly improves obstetric and neonatal outcomes for women addicted to heroin. Enrollment of a heroin-addicted pregnant woman in such a maintenance program reduces the risk of malnutrition, infection, preterm labor, spontaneous abortion, preeclampsia, eclampsia, abruptio placenta, and septic thrombophlebitis. The dosage of methadone during pregnancy should be the lowest effective dosage, and no withdrawal to abstinence should be attempted during pregnancy. Methadone is metabolized more rapidly in the third trimester, which may necessitate higher dosages. To avoid potentially sedating postdose peak plasma concentrations, the daily dose can be administered in two divided doses during the third trimester. Methadone treatment has no known teratogenic effects.

**Neonatal Methadone Withdrawal Symptoms.** Withdrawal symptoms in newborns frequently include tremor, a high-pitched cry, increased muscle tone and activity, poor sleep and eating, mottling, yawning, perspiration, and skin excoriation. Convulsions that require aggressive anticonvulsant therapy may also occur. Withdrawal symptoms may be delayed in onset and prolonged in neonates because of their immature hepatic metabolism. Women taking methadone are sometimes counseled to initiate breastfeeding as a means of gently weaning their infants from methadone dependence, but they should not breastfeed their babies while still taking methadone.

**Buprenorphine** The analgesic effects of buprenorphine are sometimes used in the management of chronic pain when less addictive agents are ineffective. Because buprenorphine is a partial agonist rather than a full agonist at the  $\mu$ -receptor and is a weak antagonist at the  $\kappa$ -receptor, this agent produces a milder withdrawal syndrome and has a wider margin of safety than the full  $\mu$ -agonist compounds generally used in treatment. Buprenorphine has a ceiling effect beyond which dose increases prolong the duration of action of the drug without further increasing the agonist effects. Because of this, buprenorphine has a high clinical safety profile, with limited respiratory depression, therefore decreasing the likelihood of lethal overdose. Buprenorphine does have the capacity to cause typical side effects associated with opioids, including sedation, nausea and vomiting, constipation, dizziness, headache, and sweating. A relevant pharmacokinetic consideration when using buprenorphine is the fact that it requires hepatic conversion to become analgesic (N-dealkylation catalyzed by CYP3A4). This may explain why some patients do not benefit from buprenorphine. Genetics, grapefruit juice, and many medications (including fluoxetine and fluvoxamine) can reduce a person's ability to metabolize buprenorphine into its bioactive form. To reduce the likelihood of abusing buprenorphine via the IV route, buprenorphine has been combined with the narcotic antagonist naloxone for sublingual administration. Because naloxone is poorly absorbed by the sublingual route, when the combination drug is taken sublingually, there is no effect of the naloxone on the efficacy of buprenorphine. If an opioid-dependent individual injects the combination medication, the naloxone precipitates a withdrawal reaction, therefore reducing the likelihood of illicit injection use of the sublingual preparation. Inducting and stabilizing a patient on buprenorphine is analogous to inducting and stabilizing a patient on methadone except that, as a partial agonist, buprenorphine has the potential to cause precipitated withdrawal in patients who have recently taken full agonist opioids. Thus, a patient must abstain from the use of short-acting opioids for 12 to 24 hours before starting buprenorphine and from longer acting opioids such as

methadone for 24 to 48 hours or longer. The physician must assess the patient clinically and determine that the patient is in mild to moderate opioid withdrawal with objectively observable withdrawal signs before initiating buprenorphine. In most instances, a relatively low dose of buprenorphine (2 to 4 mg) can then be

administered with additional doses given in 1 to 2 hours if withdrawal signs persist. The goal for the first 24 hours is to suppress withdrawal signs and symptoms, and the total 24-hour dose to do so can range from 2 to 16 mg on the first day. In subsequent days, the dose can be adjusted upward or downward to resolve withdrawal fully and, as with methadone, to achieve an absence of craving, adequate tolerance to prevent reinforcement from the use of other opioids, and ultimately abstinence from other opioids while minimizing side effects. Dose-ranging studies have demonstrated that dosages of 6 to 16 mg per day are associated with improved treatment outcomes compared with lower doses of buprenorphine (1 to 4 mg). Sometimes patients seem to need dosages higher than 16 mg per day, although there is no evidence for any benefit of dosages beyond 32 mg per day. For the treatment of opioid dependence, a dose of approximately 4 mg of sublingual buprenorphine is the equivalent of a daily dose of 40 mg of oral methadone. It has also been demonstrated that daily, alternate-day, or threetimes-per-week administration has equivalent effects in suppressing the symptoms of opioid withdrawal in dependent individuals. The combination tablet is recommended for most clinical purposes, including induction and maintenance. The buprenorphine mono should be used only for pregnant patients or for patients who have a documented anaphylactic reaction to naloxone. Newer forms of buprenorphine delivery, including a transdermal skin patch, a longacting depot intramuscular injection that provides therapeutic plasma levels for several weeks, and subcutaneous buprenorphine implants that may provide therapeutic plasma levels for 6 months, are being investigated. The last two delivery systems could obviate the need for taking medications daily while virtually eliminating the risk of medication nonadherence. Tramadol There are multiple reports of tramadol's antidepressant effects, both as monotherapy and augmentation agent in treatment-resistant depression. Clinical and experimental data suggest that tramadol has an inherent antidepressant-like activity. Tramadol has a complex pharmacology. It is a weak  $\mu$ -opioid receptor agonist, a 5-HT releasing agent, a DA-releasing agent, a 5-HT<sub>2C</sub> receptor antagonist, an norepinephrine reuptake inhibitor, an N-methyl-d-aspartate (NMDA) receptor antagonist, a nicotinic acetylcholine receptor antagonist, a TRPV1 receptor agonist and an M1 and M3 muscarinic acetylcholine receptor antagonist. Consistent with the evidence of its antidepressant effects is the fact that tramadol has a close structural similarity to the antidepressant venlafaxine. Both venlafaxine and tramadol inhibit norepinephrine/serotonin reuptake and inhibit the reserpine-induced syndrome completely. Both compounds also have an analgesic effect on chronic pain. Venlafaxine may have an opioid component, and naloxone reverses the antipain effect of venlafaxine. Nonopioid activity is demonstrated by the fact that its analgesic effect is not fully antagonized by the  $\mu$ -opioid receptor antagonist naloxone. Indicative of their structural similarities, venlafaxine may cause false-positive results on liquid chromatography tests to detect urinary tramadol levels.

Another relevant property of tramadol is its relatively long half-life, which reduces the potential for misuse. Its habituating effects are found to be much less than other opiate agonists, but abuse, withdrawal, and dependence are risks. Tramadol requires metabolism to become analgesic: individuals who are CYP2D6 "poor metabolizers" or use drugs that are CYP2D6 inhibitors reduce the efficacy of tramadol (the same is true of codeine). PRECAUTIONS AND ADVERSE REACTIONS

The most common adverse effects of opioid receptor agonists are lightheadedness, dizziness, sedation, nausea, constipation, vomiting, perspiration, weight gain, decreased libido, inhibition of orgasm, and insomnia or sleep irregularities. Opioid receptor agonists are capable of inducing tolerance as well as producing physiologic and psychological dependence. Other CNS adverse effects include depression, sedation, euphoria, dysphoria, agitation, and seizures. Delirium has been reported in rare cases. Occasional non-CNS adverse effects include peripheral edema, urinary retention, rash, arthralgia, dry mouth, anorexia, biliary tract spasm, bradycardia, hypotension, hypoventilation, syncope, antidiuretic hormone-like activity, pruritus, urticaria, and visual disturbances. Menstrual irregularities are common in women, especially in the first 6 months of use. Various abnormal endocrine laboratory indexes of little clinical significance may also be seen. Most persons develop tolerance to the pharmacologic adverse effects of opioid agonists during long-term maintenance, and relatively few adverse effects are experienced after the induction period. Overdosage The acute effects of opioid receptor agonist overdose include sedation, hypotension, bradycardia, hypothermia, respiratory suppression, miosis, and decreased GI motility. Severe effects include coma, cardiac arrest, shock, and death. The risk of overdose is greatest in the induction stage of treatment and in persons with slow drug metabolism caused by preexisting hepatic insufficiency. Deaths have been caused during the first week of induction by methadone dosages of only 50 to 60 mg a day. The risk of overdose with buprenorphine appears to be lower than with methadone. However, deaths have been caused by use of buprenorphine in combination with benzodiazepines. Withdrawal Symptoms Abrupt cessation of methadone use triggers withdrawal symptoms within 3 to 4 days, which usually reach peak intensity on the sixth day. Withdrawal symptoms include weakness, anxiety, anorexia, insomnia, gastric distress, headache, sweating, and hot and cold flashes. The withdrawal symptoms usually resolve after 2 weeks. However, a protracted methadone abstinence syndrome is possible that may include restlessness and

insomnia. The withdrawal symptoms associated with buprenorphine are similar to, but less marked than, those caused by methadone. In particular, buprenorphine is sometimes used to ease the transition from methadone to opioid receptor antagonists or abstinence because of the relatively mild withdrawal reaction associated with discontinuation of buprenorphine. DRUG-DRUG INTERACTIONS Opioid receptor agonists can potentiate the CNS-depressant effects of alcohol, barbiturates, benzodiazepines, other opioids, low-potency dopamine receptor antagonists, tricyclic and tetracyclic drugs, and MAOIs. Carbamazepine (Tegretol), phenytoin (Dilantin), barbiturates, rifampin (Rimactane, Rifadin), and heavy long-term consumption of alcohol may induce hepatic enzymes, which may lower the plasma concentration of methadone or buprenorphine and thereby precipitate withdrawal symptoms. In contrast, however, hepatic enzyme induction may increase the plasma concentration of active levomethadyl metabolites and cause toxicity. Acute opioid withdrawal symptoms may be precipitated in persons on methadone maintenance therapy who take pure opioid receptor antagonists such as naltrexone, nalmefene (Revex), and naloxone (Narcan); partial agonists such as buprenorphine; or mixed agonist-antagonists such as pentazocine (Talwin). These symptoms may be mitigated by use of clonidine, a benzodiazepine, or both. Competitive inhibition of methadone or buprenorphine metabolism after short-term use of alcohol or administration of cimetidine (Tagamet), erythromycin, ketoconazole (Nizoral), fluoxetine (Prozac), fluvoxamine (Luvox), loratadine (Claritin), quinidine (Quinidex), and alprazolam (Xanax) may lead to higher plasma concentrations or a prolonged duration of action of methadone or buprenorphine. Medications that alkalinize the urine may reduce methadone excretion. Methadone

maintenance may also increase plasma concentrations of desipramine (Norpramin, Pertofrane) and fluvoxamine. Use of methadone may increase zidovudine (Retrovir) concentrations, which increases the possibility of zidovudine toxicity at otherwise standard dosages. Moreover, in vitro human liver microsome studies demonstrate competitive inhibition of methadone demethylation by several protease inhibitors, including ritonavir (Norvir), indinavir (Crixivan), and saquinavir (Invirase). The clinical relevance of this finding is unknown. Fatal drug-drug interactions with the MAOIs are associated with use of the opioids fentanyl (Sublimaze) and meperidine (Demerol) but not with use of methadone, levomethadyl, or buprenorphine. Tramadol may interact with drugs that inhibit serotonin reuptake. Such combinations can trigger seizures and serotonin syndrome. These events may also develop during tramadol monotherapy, either at routine or excessive doses. Risk of interactions is increased when tramadol is combined with virtually all classes of antidepressants and with drugs that lower the seizure threshold, especially the antidepressant bupropion.

**LABORATORY INTERFERENCES** Methadone and buprenorphine can be tested for separately in urine toxicology to distinguish them from other opioids. No known laboratory interferences are associated with the use of methadone or buprenorphine.

**DOSAGE AND CLINICAL GUIDELINES**

**Methadone** Methadone is supplied in 5-, 10-, and 40-mg dispersible scored tablets; 40-mg scored wafers; 5-mg/5-mL, 10-mg/5-mL, and 10-mg/mL solutions; and a 10-mg/mL parenteral form. In maintenance programs, methadone is usually dissolved in water or juice, and dose administration is directly observed to ensure compliance. For induction of opioid detoxification, an initial methadone dose of 15 to 20 mg will usually suppress craving and withdrawal symptoms. However, some individuals may require up to 40 mg a day in single or divided doses. Higher dosages should be avoided during induction of treatment to reduce the risk of acute toxicity from overdose. Over several weeks, the dosage should be raised to at least 70 mg a day. The maximum dosage is usually 120 mg a day, and higher dosages require prior approval from regulatory agencies. Dosages above 60 mg a day are associated with much more complete abstinence from use of illicit opioids than are dosages less than 60 mg a day. The duration of treatment should not be predetermined but should be based on response to treatment and assessment of psychosocial factors. All studies of methadone maintenance programs endorse long-term treatment (i.e., several years) as more effective than short-term programs (i.e., less than 1 year) for prevention of relapse into opioid abuse. In actual practice, however, a minority of programs are permitted by policy or approved by insurers to provide even 6 months of continuous maintenance treatment. Moreover, some programs actually encourage withdrawal from methadone in less than 6 months after induction. This is quite ill conceived because more than 80 percent of persons who terminate methadone maintenance treatment eventually return to illicit drug use within 2 years. In programs that offer both maintenance and withdrawal treatments, the overwhelming majority of participants enroll in the maintenance treatment.

**Buprenorphine** Buprenorphine is supplied as a 0.3-mg/mL solution in 1-mL ampules. Sublingual tablet formulations of buprenorphine containing buprenorphine only or buprenorphine combined with naloxone in a 4:1 ratio are used for opioid maintenance treatment. Buprenorphine is not used for short-term opioid detoxification. Maintenance dosages of 8 to 16 mg thrice weekly have effectively reduced heroin use. Physicians must be trained and certified to carry out this therapy in their private offices. There are a number of approved training programs in the United States.

**Tramadol** There are no controlled trials establishing the appropriate dosing schedule for tramadol when used for conditions other than pain. Tramadol is available in many formulations. These range

from capsules (regular and extended release) to tablets (regular, extended release, chewable tablets) that can be taken sublingually, suppositories and injectable ampules. It also comes as tablets and capsules containing acetaminophen or aspirin. Doses in case reports of treatment for depression or OCD range from 50 to 200 mg a day and involve short-term use. The long-term use of tramadol in the treatment of psychiatric disorders has not been studied. REFERENCES Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs. buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: A randomized trial. *JAMA*. 2005;294(8):903. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D. Drug-induced long QT syndrome in injection drug users receiving methadone: High frequency in hospitalized patients and risk factors. *Arch Intern Med*. 2006;166(12):1280. Fiellin DA, Moore BA, Sullivan LE, Becker WC, Pantalon MV, Chawarski MC, Barry DT, O'Connor PG, Schottenfeld RS. Long-term treatment with buprenorphine/naloxone in primary care: Results at 2-5 years. *Am J Addict*. 2008;17:116. Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces longterm mortality. *Addiction*. 2008;103:462. Gryczynski J, Jaffe JH, Schwartz RP, et al. Patient perspectives on choosing buprenorphine over methadone in an urban, equal-access system. *Am J Addict*. 2013;22(3):285-291. Heit HA, Gourlay DL. Buprenorphine: New tricks with an old molecule for pain management. *Clin J Pain*. 2008;24:93. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001;58:503. Kleber HD. Methadone maintenance 4 decades later: Thousands of lives saved but still controversial. *JAMA*. 2008;300:2303. Likar R, Kayser H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: A multicenter, openlabel, follow-up study in patients from three short-term clinical trials. *Clin Ther*. 2006;28(6):943. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008:CD002207. Neumann AM, Blondell RD, Jaanimagi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis*. 2013;32(1):68-78. Oliva EM, Trafton JA, Harris AH, Gordon AJ. Trends in opioid agonist therapy in the Veterans Health Administration: Is supply keeping up with demand? *Am J Drug Alcohol Abuse*. 2013;39(2):103-107. Saxon AJ, McRae-Clark AL, Brady KT. Opioid receptor agonists: Methadone and buprenorphine. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th edition. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3171. Savage SR. Principles of pain treatment in the addicted patient. In: Graham AW, Schultz TK, eds. *Principles of Addiction Medicine*. 2nd edition. Chevy Chase, MD: American Society of Addiction Medicine; 1998:919. Sigmon SC, Moody DE, Nuwayser ES, Bigelow GE. An injection depot formulation of buprenorphine: Extended biodelivery and effects. *Addiction*. 2006;101(3):420.

---

Revision #1

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

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