SUBSTANCE USE DISORDER AGENT

# Naltrexone

ReVia, Vivitrol, Contrave (with bupropion)

*Opioid receptor antagonist that is first-line pharmacotherapy for alcohol use disorder and an abstinence-based option for opioid use disorder.*

| USUAL ADULT DOSE | HALF-LIFE | METABOLISM | ONSET |
|---|---|---|---|
| 50 mg/day PO or 380 mg IM q4wks | 4 h PO; 5-10 days IM depot | Non-CYP hepatic; 6-beta-naltrexol | Opioid blockade within 1 h PO |

**No FDA boxed warning** on the current US label.

## INDICATIONS

- FDA-approved for alcohol use disorder in adults, cutting heavy drinking days and relapse risk; oral **50 mg/day** or extended-release **380 mg** IM monthly.
- FDA-approved for blockade of exogenous opioid effects and prevention of relapse to opioid dependence in adults after complete opioid detoxification.
- Extended-release injectable naltrexone matched buprenorphine-naloxone on relapse in the X:BOT trial once induction succeeded, but induction failed far more often.
- Off-label with bupropion for methamphetamine use disorder, the regimen tested in ADAPT-2; response rates are modest but clearly exceed placebo.
- Off-label for gambling disorder, kleptomania, trichotillomania and self-injurious behavior in intellectual disability, on small-trial evidence only.
- Marketed with bupropion as **Contrave** for chronic weight management; naltrexone alone is not indicated for obesity or for smoking cessation.

## DOSING & TITRATION

- Confirm the patient is opioid-free for **7-10 days** (10-14 days after methadone) and consider a naloxone challenge or urine screen before dose one.
- Oral: start **25 mg** once daily for one to two days to test tolerability, then **50 mg** daily; alternate-day **100 mg** dosing can support observed therapy.
- Extended-release: **380 mg** IM into the gluteal muscle every 4 weeks, alternating sides, using only the supplied needle, diluent and technique.
- For alcohol use disorder treatment may begin while the patient is still drinking; abstinence is not required before the first dose.
- No taper is needed on discontinuation, but opioid tolerance is lost during treatment, so counsel on overdose risk and dispense take-home naloxone.
- No adjustment for mild to moderate hepatic or renal impairment; avoid in acute hepatitis or hepatic failure and use caution in severe renal disease.

## MECHANISM OF ACTION

- Competitive antagonist at mu-opioid receptors with weaker kappa and delta blockade, abolishing euphoria and analgesia from full opioid agonists.
- In alcohol use disorder it blunts the endogenous opioid surge triggered by drinking, reducing alcohol-induced reward and cue-driven craving.
- The effect falls mainly on heavy drinking days and drinks per occasion rather than on total abstinence, so patients can drink through it.
- No agonist activity at any dose, so there is no euphoria, no tolerance, no physical dependence and no withdrawal syndrome on stopping.
- OPRM1 A118G genotype may predict a stronger response to naltrexone, but pharmacogenetic testing is not part of routine practice.

## PHARMACOKINETICS

- Oral absorption is nearly complete but heavy first-pass metabolism leaves roughly **5-40%** bioavailability; food does not require a dose change.
- Metabolized by hepatic dihydrodiol dehydrogenase rather than CYP450 to the active metabolite 6-beta-naltrexol, which circulates far longer.
- Plasma half-life is about **4 h** for naltrexone and **13 h** for 6-beta-naltrexol; a **50 mg** oral dose blocks opioid receptors for roughly 24 h.
- The intramuscular suspension peaks at 2 h and again at 2-3 days, then delivers sustained exposure with an apparent half-life of 5-10 days.
- Excreted renally as metabolites; compensated cirrhosis raises exposure several-fold, and there are no data in severe renal impairment.

## ADVERSE EFFECTS

- Nausea in roughly **10-33%**, plus headache, dizziness, fatigue, insomnia and anxiety, are the usual early complaints and fade over one to two weeks.
- Injection-site reactions affect up to **50%** of depot recipients; induration, cellulitis, sterile abscess and rare necrosis need prompt evaluation.
- Dose-related transaminase elevation occurs; the old hepatotoxicity boxed warning was removed in 2013, but liver monitoring remains prudent.
- Opioid analgesia is blocked, so emergency pain control requires regional anesthesia, non-opioid agents or titrated opioids with airway monitoring.
- Precipitated withdrawal follows dosing in an opioid-dependent patient and is prolonged and severe with the depot because it cannot be removed.
- Depressed mood and suicidal ideation have been reported; monitor mood, recognizing that untreated substance use disorder itself carries this risk.

## MONITORING

- Baseline liver function tests and periodic transaminases, especially with hepatitis C, alcohol-related liver disease or other hepatotoxic drugs.
- Urine drug screen covering opioids, oxycodone, methadone and buprenorphine before initiation and before each depot injection.
- Pregnancy test in people of childbearing potential, a baseline renal panel, and inspection of injection sites at every depot visit.
- Track drinking days, heavy drinking days and craving using the timeline followback, AUDIT-C or the Penn Alcohol Craving Scale.
- Reassess at 3 months; if heavy drinking persists despite adherence, consider acamprosate, disulfiram or off-label topiramate.

## INTERACTIONS & CAUTIONS

- Contraindicated with any full opioid agonist, including methadone, buprenorphine, codeine-containing cough syrups and antidiarrheals such as loperamide.
- Blocks opioid analgesics and antitussives; flag naltrexone status before elective surgery and stop the oral drug at least 72 h beforehand.
- Additive hepatic risk with high-dose acetaminophen, isoniazid, methotrexate or continued heavy alcohol use warrants closer transaminase checks.
- The bupropion combination lowers seizure threshold; avoid in seizure disorder, bulimia, anorexia nervosa and abrupt sedative or alcohol withdrawal.
- No clinically significant CYP450 interactions, which makes naltrexone easy to combine with antidepressants, antipsychotics and mood stabilizers.

## SPECIAL POPULATIONS

- Pregnancy: human data are limited; methadone or buprenorphine remains preferred for opioid use disorder, though stable patients may continue naltrexone.
- Lactation: small amounts enter milk and the depot is less preferred; monitor the infant for sedation and poor feeding if treatment continues.
- Pediatric safety and effectiveness are not established; adolescent use for alcohol or opioid use disorder is off-label and supported by small series.
- Geriatric data are sparse; use standard doses but screen for hepatic and renal impairment, sedation and fall risk before starting the depot.
- Hepatic: contraindicated in acute hepatitis or hepatic failure; compensated cirrhosis substantially raises exposure and calls for closer follow-up.

## PRESCRIBING PEARLS

- Opioid tolerance is lost on naltrexone, so overdose risk spikes after stopping; send naloxone home.
- The depot cannot be removed, so document **7-10 days** opioid-free before the first injection.
- It reduces heavy drinking more than it produces abstinence; continue it through a lapse.

# References

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**NOTE**

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.