SUBSTANCE USE DISORDER AGENT | C-II

Methadone

Dolophine, Methadose, Diskets

Long-acting full mu-opioid agonist for opioid use disorder and severe chronic pain; highly effective and the most dangerous drug to initiate.

USUAL OUD DOSE	HALF-LIFE	METABOLISM	STEADY STATE
60-120 mg/day PO	8-59 h; analgesia only 4-8 h	CYP3A4, 2B6, 2C19, 2D6, 2C9	3-10 days after a change

⚠ FDA BOXED WARNING

Addiction, abuse and misuse; life-threatening respiratory depression, especially at initiation; fatal accidental ingestion, notably by children; QT prolongation and torsades; neonatal opioid withdrawal syndrome; profound sedation and death with benzodiazepines or CNS depressants; CYP inducer and inhibitor interactions.

INDICATIONS

- FDA-approved for detoxification and maintenance treatment of opioid use disorder in adults, which outside hospital may be dispensed only by certified opioid treatment programs.
- FDA-approved for pain severe enough to require daily around-the-clock long-term opioid treatment when alternative options are inadequate.
- For pain, any DEA-registered prescriber may write for methadone; the opioid treatment program restriction applies only to addiction treatment.
- Any hospital may administer methadone to an admitted patient already in treatment, or for withdrawal while treating another condition.
- Retention in treatment and mortality reduction at least equal buprenorphine, with better retention at doses of **60 mg/day** or more.
- The 2024 revision of 42 CFR Part 8 made pandemic take-home flexibilities permanent and allows audio-visual telehealth initiation.

DOSING & TITRATION

- Opioid use disorder induction: first dose **20-30 mg**, no single dose above 30 mg, and no more than **40 mg** total on day 1 with reassessment at 2-4 h.
- Increase by no more than **5-10 mg** every 3-5 days at the fastest, because deaths cluster in the first two weeks when levels are still accumulating.
- Effective maintenance is usually **60-120 mg/day** as a single daily dose; some patients need more, guided by response, not by an arbitrary ceiling.
- Chronic pain in an opioid-naive adult starts at **2.5 mg every 8 h**; never dose every 4-6 h, and never convert from morphine using a fixed ratio.
- Rotation from another opioid requires published dose-dependent tables and a **75-90%** reduction from the calculated equianalgesic dose.
- Taper slowly if stopping, on the order of 10% per month for maintenance patients; indefinite maintenance is a legitimate and usually preferable outcome.

MECHANISM OF ACTION

- Full mu-opioid receptor agonist with no ceiling effect, so respiratory depression rises steadily with dose and with any added sedative.
- NMDA receptor antagonism contributes to analgesia in neuropathic and opioid-tolerant pain and may blunt the development of tolerance.
- Inhibits serotonin and norepinephrine reuptake, which underlies a real if uncommon serotonin syndrome risk with serotonergic agents.
- Blocks the hERG potassium channel in a dose-dependent way, prolonging the QT interval and creating torsades de pointes risk.
- Long and variable elimination greatly outlasts analgesia, so tissue stores build for days after each dose increase before the effect plateaus.

PHARMACOKINETICS

- Oral bioavailability is high at roughly **70-80%** and highly variable, with extensive binding to alpha-1-acid glycoprotein in plasma.
- Elimination half-life ranges from **8 to 59 h** across patients while analgesia lasts only 4-8 h, the mismatch that drives fatal dose stacking.
- Steady state is not reached for **3-10 days**, so the full effect of any increase is not visible when the next increase is usually considered.
- Metabolized by CYP3A4, 2B6, 2C19, 2D6 and 2C9 to inactive EDDP; CYP2B6 genotype shifts levels of the more cardiotoxic S-enantiomer.
- Excreted in urine and feces with pH-dependent renal clearance; methadone is not removed by hemodialysis, so dialysis does not rescue overdose.

ADVERSE EFFECTS

- Constipation, sweating in up to **45%**, sedation, nausea, weight gain, dry mouth and peripheral edema are the routine ongoing complaints.
- QTc prolongation is dose-related and clinically important above roughly **100 mg/day**, with torsades de pointes reported at maintenance doses.
- Respiratory depression and death occur most often during induction and after dose increases, and often at night during sleep.
- Central and obstructive sleep apnea appear in a substantial minority at higher doses and worsen nocturnal hypoxemia.
- Opioid-induced androgen deficiency causes low libido, erectile dysfunction, amenorrhea, fatigue and reduced bone density over time.
- Neonatal opioid withdrawal syndrome is expected after third-trimester exposure and is treatable, but requires delivery where neonatology is available.

MONITORING

- ECG at baseline, at about 30 days, then annually and after any dose exceeding **100 mg/day** or the addition of a QT-prolonging drug.
- Potassium and magnesium, particularly in patients on diuretics, with vomiting or diarrhea, or with cardiac or hepatic disease.
- Observed daily dosing at first, with take-home doses granted according to the 42 CFR Part 8 criteria as stability is established.
- Sedation and respiratory rate reassessed 2-4 h after dosing during induction, plus screening questions for snoring and witnessed apnea.
- Urine drug testing, prescription drug monitoring program review, and testosterone or menstrual history when symptoms suggest hypogonadism.

INTERACTIONS & CAUTIONS

- Benzodiazepines, alcohol, gabapentinoids and other CNS depressants markedly raise overdose risk, though FDA warns against withholding methadone for benzodiazepine use alone.
- CYP inducers such as rifampin, carbamazepine, phenytoin, efavirenz and St. John's wort cause withdrawal, and overdose when the inducer is stopped.
- CYP inhibitors including fluvoxamine, fluconazole, ciprofloxacin, clarithromycin and some antiretrovirals raise levels and QT risk.
- Additive QT prolongation with ondansetron, haloperidol, citalopram, quetiapine, azoles, macrolides and fluoroquinolones warrants ECG review.
- Buprenorphine, naltrexone and other antagonists or partial agonists precipitate withdrawal, and MAOIs are contraindicated within 14 days.

SPECIAL POPULATIONS

- Pregnancy: methadone remains a standard of care; dose requirements usually rise in the third trimester and split twice-daily dosing often helps.
- Lactation: milk concentrations are low and breastfeeding is encouraged in stable patients, with the infant watched for sedation and poor feeding.
- Pediatric: safety and effectiveness for opioid use disorder are not established under 18, and federal rules add consent requirements for minors.
- Geriatric patients are more sensitive to respiratory depression, QT effects and falls; start at the low end and lengthen the titration interval.
- Hepatic or renal impairment: reduce the dose and titrate more slowly in severe disease; hemodialysis does not remove methadone from the body.

☆ PRESCRIBING PEARLS

- Analgesia lasts 4-8 h but the drug lingers for days; every 4 h pain dosing stacks and kills.
- Deaths cluster in the first two weeks: raise by **5-10 mg** no faster than every 3-5 days.
- Outpatient dosing for opioid use disorder is legal only through a certified treatment program.

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.