ATYPICAL ANTIDEPRESSANT

Trazodone

Desyrel, Oleptro (brands discontinued; generics available)

Serotonin antagonist and reuptake inhibitor approved for depression but used almost entirely off-label at low doses for insomnia.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
150-400 mg/day PO for MDD	3-6 h, then 5-9 h terminal	CYP3A4; active mCPP metabolite	Sleep night 1; mood 2-4 wks

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk of suicidality in pediatric and young adult patients in short-term studies. Closely monitor all treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Not approved for use in pediatric patients.

INDICATIONS

- FDA-approved for major depressive disorder in adults at **150-400 mg/day** in divided doses, taken shortly after a meal.
- Antidepressant doses are poorly tolerated because of sedation and orthostasis, so trazodone is rarely used as monotherapy for depression.
- Off-label at **25-100 mg** at bedtime for insomnia, which accounts for the large majority of trazodone prescriptions written today.
- The American Academy of Sleep Medicine recommends against trazodone for chronic insomnia, citing weak evidence and adverse effects.
- Off-label for insomnia complicating SSRI or stimulant treatment, where it avoids the dependence liability of benzodiazepine receptor agonists.
- Off-label for agitation in dementia and for PTSD-related insomnia, though the supporting evidence in both settings is limited.

DOSING & TITRATION

- For depression start **150 mg/day** in divided doses, increase by 50 mg/day every three to four days, to a maximum of **400 mg/day** in outpatients.
- Inpatients with severe depression may be titrated to **600 mg/day** in divided doses under close blood pressure monitoring.
- For off-label insomnia start at 25 to 50 mg at bedtime and increase to no more than 100 mg, since higher doses add hangover without added hypnotic effect.
- Available as 50, 100, 150, and 300 mg immediate-release tablets; the extended-release formulation is no longer marketed in the United States.
- Reduce the dose and titrate slowly in older adults and in hepatic impairment, where clearance is meaningfully reduced.
- Taper gradually from antidepressant doses; low bedtime hypnotic doses can usually be stopped without a formal taper.

MECHANISM OF ACTION

- Acts as a serotonin antagonist and reuptake inhibitor, with potent 5-HT2A blockade and comparatively weak serotonin transporter inhibition.
- At low doses 5-HT2A, histamine H1, and alpha-1 blockade dominate, which is why 25 to 100 mg produces sedation without antidepressant effect.
- Antidepressant efficacy requires doses high enough to engage the serotonin transporter, generally at or above **150 mg/day**.
- Alpha-1 adrenergic blockade causes orthostatic hypotension and dizziness and is the mechanism behind trazodone-associated priapism.
- Its metabolite meta-chlorophenylpiperazine is a serotonin agonist that can provoke anxiety and dysphoria when it accumulates.

PHARMACOKINETICS

- Absorption is improved and peak concentrations are blunted when taken shortly after a meal, which reduces dizziness and lightheadedness.
- Elimination is biphasic, with an initial phase of about **3 to 6 hours** and a terminal phase of roughly 5 to 9 hours.
- The short initial phase suits sleep onset but can leave residual grogginess when higher doses are given late at night.
- Metabolized principally by CYP3A4 to meta-chlorophenylpiperazine, which is then cleared by CYP2D6 and accumulates in poor metabolizers.
- It is 89 to 95 percent protein bound, and clearance falls in older adults, hepatic impairment, and significant renal impairment.

ADVERSE EFFECTS

- Somnolence and sedation occur in roughly 40 percent of patients at antidepressant doses and are the intended effect at hypnotic doses.
- Orthostatic hypotension and dizziness are common, mediated by alpha-1 blockade, and contribute directly to falls in older adults.
- Priapism occurs in approximately **1 in 6000** treated men and is a urologic emergency, with about one third of reported cases requiring surgery.
- QT prolongation and rare torsades de pointes have been reported, so it should be used cautiously with other QT-prolonging drugs.
- Dry mouth, blurred vision, nausea, headache, and cognitive dulling are frequent, while sexual dysfunction is uncommon.
- Serotonin syndrome, hyponatremia, and treatment-emergent mania apply as with other serotonergic antidepressants.

MONITORING

- Counsel every male patient about priapism before starting and instruct them to seek emergency care for an erection lasting over four hours.
- Check orthostatic blood pressure at baseline and after dose increases, especially in older adults and patients on antihypertensives.
- Assess suicidality, activation, and daytime sedation weekly for the first four weeks and after each dose change.
- Obtain an ECG in patients with cardiac disease, electrolyte disturbance, or concurrent QT-prolonging medications.
- Check serum sodium at baseline and within two to four weeks in older adults or those taking diuretics.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP3A4 inhibitors such as ritonavir, ketoconazole, and clarithromycin raise trazodone levels and require a dose reduction.
- Strong CYP3A4 inducers including carbamazepine and rifampin can lower concentrations substantially and blunt the hypnotic effect.
- Additive sedation and hypotension with alcohol, opioids, benzodiazepines, antihypertensives, and alpha-blockers used for prostatism.
- Additive QT risk with methadone, antipsychotics, ondansetron, and class III antiarrhythmics, and additive serotonergic risk with SSRIs and triptans.

SPECIAL POPULATIONS

- Pregnancy data are limited but do not show a clear teratogenic signal; better-studied agents are preferred when depression is the target.
- Relative infant dose in breast milk is low, under 3 percent, so occasional bedtime use is generally considered acceptable.
- Not approved in pediatrics, and pediatric insomnia use is off-label with essentially no controlled efficacy evidence.
- In older adults start at **25 mg** at bedtime and weigh fall risk carefully, since orthostasis and sedation are the dominant hazards.
- Reduce the dose in hepatic impairment and use caution in significant renal impairment, where metabolites can accumulate.

PRESCRIBING PEARLS

- Below 150 mg/day it is a hypnotic, not an antidepressant; the transporter is barely engaged.
- Warn every man about priapism, roughly 1 in 6000, and give clear instructions to seek emergency care.
- AASM recommends against it for chronic insomnia despite its being the most prescribed sleep agent.

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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.