TRICYCLIC ANTIDEPRESSANT

Desipramine

Norpramin

The most noradrenergic-selective and least anticholinergic tricyclic, useful when sedation and antimuscarinic load must be minimized.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
100-200 mg/day PO	12-27 h (mean about 22 h)	CYP2D6 major, CYP1A2 minor	2-4 wks; 6 wks full effect

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Monitor closely for clinical worsening and emergence of suicidality, especially early in treatment and after dose changes.

INDICATIONS

- FDA-approved for the relief of symptoms of depression in adults, particularly endogenous depression with prominent psychomotor retardation.
- Off-label for painful diabetic neuropathy and postherpetic neuralgia, where it matches amitriptyline with less anticholinergic burden.
- Off-label for attention-deficit hyperactivity disorder in adults and adolescents when stimulants are ineffective or contraindicated.
- Off-label for binge-eating and bulimia nervosa, though selective serotonin reuptake inhibitors remain the preferred first-line agents.
- A reasonable tricyclic choice for patients who need noradrenergic activation without the sedation of amitriptyline or doxepin.
- Not established as safe or effective in pediatric patients, and reports of sudden death in children argue strongly against routine use.

DOSING & TITRATION

- Start **25-50 mg/day PO** in adults, often as a single morning or bedtime dose, and increase by 25 mg every 2 to 3 days as tolerated.
- Usual effective range is **100-200 mg/day**; if no response after 2 weeks at that dose, obtain a plasma level before escalating further.
- Maximum is **300 mg/day** in hospitalized patients under supervision; outpatients should generally not exceed **200 mg/day**.
- In older or adolescent patients start at **10-25 mg/day** and keep the total below **150 mg/day** unless levels justify more.
- Supplied as 10, 25, 50, 75, 100, and 150 mg tablets; no formal renal adjustment exists but hepatic impairment requires lower doses.
- Taper over several weeks when stopping, because abrupt withdrawal causes nausea, headache, malaise, insomnia, and restlessness.

MECHANISM OF ACTION

- The active demethylated metabolite of imipramine, acting almost purely as a norepinephrine reuptake inhibitor with minimal serotonergic effect.
- Muscarinic affinity is the lowest of the tricyclics, so dry mouth, constipation, and cognitive clouding are comparatively mild.
- Weak histamine H1 blockade means little sedation or weight gain, which makes morning dosing feasible and sometimes preferable.
- Alpha-1 adrenergic antagonism is modest, giving less orthostatic hypotension than tertiary amines but more than nortriptyline.
- Enhanced noradrenergic tone in descending spinal pathways underlies analgesia, while sodium channel blockade drives overdose cardiotoxicity.

PHARMACOKINETICS

- Well absorbed orally with peak plasma concentrations at roughly 4 to 6 hours; food does not meaningfully alter absorption.
- Elimination half-life averages about 22 hours with a range of 12 to 27 hours, supporting once-daily dosing at steady state.
- Hydroxylated principally by CYP2D6 to 2-hydroxydesipramine, which retains some activity and accumulates when renal clearance falls.
- CYP2D6 poor metabolizers show markedly elevated concentrations, and CPIC recommends a 50 percent dose reduction with level monitoring.
- Highly protein bound with a large volume of distribution; hemodialysis is ineffective and overdose care is supportive and cardiac-directed.

ADVERSE EFFECTS

- Anticholinergic effects occur but are the mildest of the class; dry mouth and constipation are still reported by many patients.
- Activation, insomnia, jitteriness, and tachycardia reflect noradrenergic tone and may require morning dosing or slower titration.
- Orthostatic hypotension, dizziness, and falls are less frequent than with tertiary amines but remain relevant in older adults.
- Dose-dependent conduction delay prolongs PR, QRS, and QT intervals; overdose causes wide-complex arrhythmia, seizures, and shock.
- Sudden unexplained death has been reported in children receiving desipramine, which is why pediatric use is strongly discouraged.
- Weight gain and sexual dysfunction occur, and rare agranulocytosis, hepatitis, or hyponatremia have been described in the label.

MONITORING

- Therapeutic plasma concentrations are generally cited as **115-300 ng/mL**, with toxicity risk rising sharply above 300 ng/mL.
- Draw a trough level 10 to 14 hours after the dose and at least 5 days after any change so that steady state has been reached.
- Obtain a baseline ECG in patients over 50 years and in anyone with cardiac disease, then repeat after reaching the target dose.
- Monitor pulse and orthostatic blood pressure at each visit, since the noradrenergic profile can raise heart rate meaningfully.
- Watch closely for emergent suicidality, agitation, and manic switch during the first weeks and after each dose increase.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of hypertensive crisis and serotonin syndrome.
- Strong CYP2D6 inhibitors such as fluoxetine, paroxetine, bupropion, and quinidine can multiply levels several-fold and require dose reduction.
- Enzyme inducers including carbamazepine, phenytoin, rifampin, and cigarette smoking reduce concentrations and may cause treatment failure.
- Additive QT prolongation with methadone, ondansetron, and class IA or III antiarrhythmics; sympathomimetics may cause additive tachycardia.
- Antagonizes clonidine and guanfacine antihypertensive effects, and sedatives or alcohol add to central nervous system depression.

SPECIAL POPULATIONS

- Pregnancy safety is not established; limited data show no clear teratogenic pattern, but neonatal adaptation problems can follow late exposure.
- Small amounts appear in breast milk and infant plasma levels are usually undetectable, though nortriptyline has more lactation data.
- Pediatric use is not recommended given absent efficacy data in child depression and reports of sudden cardiac death in this age group.
- Beers Criteria flag all tricyclics in adults 65 and older; if desipramine is used, start at **10-25 mg** and monitor levels and ECG.
- Reduce the dose in hepatic impairment, and titrate cautiously in chronic kidney disease because hydroxy metabolites accumulate.

☆ PRESCRIBING PEARLS

- Most activating tricyclic; dose in the morning when insomnia or daytime sedation is the problem.
- Least anticholinergic of the class, but overdose is still as cardiotoxic as any other TCA.
- Reports of sudden death in children make pediatric use hard to justify.

References

American Psychiatric Association. (2010). *Practice guideline for the treatment of patients with major depressive disorder* (3rd ed.). American Psychiatric Publishing. https://psychiatryonline.org/guidelines

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Hicks, J. K., Sangkuhl, K., Swen, J. J., Ellingrod, V. L., Muller, D. J., Shimoda, K., Bishop, J. R., Kharasch, E. D., Skaar, T. C., Gaedigk, A., Dunnenberger, H. M., Klein, T. E., Caudle, K. E., & Stingl, J. C. (2017). Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clinical Pharmacology and Therapeutics, 102*(1), 37-44. https://doi.org/10.1002/cpt.597

National Institute for Health and Care Excellence. (2022). *Depression in adults: Treatment and management* (NICE Guideline NG222). https://www.nice.org.uk/guidance/ng222

Sanofi-Aventis U.S. LLC. (2023). *Norpramin (desipramine hydrochloride) tablets [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Stahl, S. M. (2021). *Stahl's essential psychopharmacology* (5th ed.). Cambridge University Press.

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.