TRICYCLIC ANTIDEPRESSANT

Imipramine

Tofranil, Tofranil-PM (imipramine pamoate)

The original tricyclic, still the reference antidepressant for panic disorder and the only TCA labeled for childhood enuresis.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
75-200 mg/day PO	11-25 h; active desipramine	CYP2D6, CYP1A2, CYP2C19, 3A4	2-4 wks; enuresis in days

⚠ 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, with endogenous depression responding better than reactive presentations.
- FDA-approved as temporary adjunctive therapy for nocturnal enuresis in children 6 years and older after organic causes are excluded.
- Off-label but strongly evidence-based for panic disorder, where it was the comparator in the foundational trials of the 1980s and 1990s.
- Off-label for generalized anxiety disorder, with randomized trial support showing benefit comparable to benzodiazepines after several weeks.
- Off-label for chronic neuropathic pain and for adjunctive treatment of attention-deficit hyperactivity disorder when stimulants fail.
- Tofranil-PM capsules are for adult use only and are specifically not indicated for children of any age.

DOSING & TITRATION

- For depression start **25-75 mg/day PO** in divided doses or at bedtime, increasing by 25 mg every few days toward **75-200 mg/day**.
- Outpatient maximum is **200 mg/day**; hospitalized patients under close supervision may receive up to **300 mg/day** if clearly needed.
- For enuresis in children 6 years and older, give **25 mg PO** one hour before bedtime; if needed raise to 50 mg under 12 years or 75 mg above 12 years.
- Pediatric enuresis dosing must not exceed **2.5 mg/kg/day**, and the drug should be tapered rather than stopped abruptly after a course.
- Available as 10, 25, and 50 mg hydrochloride tablets plus 75, 100, 125, and 150 mg pamoate capsules for once-daily adult dosing.
- Taper gradually when discontinuing; abrupt cessation produces cholinergic rebound with nausea, headache, insomnia, and vivid dreams.

MECHANISM OF ACTION

- Blocks both serotonin and norepinephrine reuptake transporters; demethylation to desipramine shifts the balance toward noradrenergic activity.
- Antimuscarinic activity at the bladder detrusor plus altered sleep architecture explains the antienuretic effect independent of mood change.
- Histamine H1 blockade contributes sedation and weight gain, while alpha-1 blockade produces orthostatic hypotension and reflex tachycardia.
- Chronic dosing downregulates beta-adrenergic and serotonin 5-HT2 receptors, a change whose timing parallels the 2 to 4 week clinical response.
- Sodium channel blockade at high concentrations widens the QRS complex and lowers the seizure threshold, driving overdose morbidity.

PHARMACOKINETICS

- Rapidly absorbed orally with substantial first-pass metabolism; peak concentrations occur about 1 to 2 hours after an immediate-release dose.
- Half-life is roughly 11 to 25 hours for the parent drug and longer for desipramine, its pharmacologically active demethylated metabolite.
- Demethylation is mediated by CYP1A2, CYP2C19, and CYP3A4, while both imipramine and desipramine are hydroxylated by CYP2D6.
- CYP2D6 poor metabolizers accumulate drug and require a 50 percent dose reduction per CPIC guidance, with plasma level confirmation.
- Extensively protein bound with a large volume of distribution and predominantly renal excretion of inactive glucuronidated metabolites.

ADVERSE EFFECTS

- Anticholinergic effects predominate, with dry mouth, constipation, blurred vision, and urinary retention limiting dose escalation.
- Orthostatic hypotension is more pronounced than with secondary amines and is a leading cause of falls and treatment discontinuation.
- Sedation, weight gain, and sexual dysfunction are common and account for much of the long-term nonadherence with this agent.
- Dose-dependent PR, QRS, and QT prolongation occurs; overdose produces wide-complex tachycardia, seizures, and refractory hypotension.
- Seizure risk rises with dose and with concurrent proconvulsants; mania may be precipitated in patients with undiagnosed bipolar disorder.
- Rare but serious reactions include agranulocytosis, eosinophilia, cholestatic jaundice, and syndrome of inappropriate antidiuretic hormone.

MONITORING

- Combined imipramine plus desipramine plasma concentration above **200-250 ng/mL** is the usual therapeutic threshold for antidepressant effect.
- Levels above roughly 300 ng/mL correlate with cardiac conduction delay and toxicity, so check a level before exceeding **200 mg/day**.
- Obtain a baseline ECG in adults over 50 years, in any cardiac disease, and in all children treated for enuresis before dose escalation.
- Track orthostatic vital signs, weight, and anticholinergic symptoms at each visit during titration and periodically during maintenance.
- Monitor closely for emergent suicidality, agitation, or mood switch during the first weeks and after every dose adjustment.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and for 14 days after stopping one because of hypertensive crisis and serotonin syndrome.
- Strong CYP2D6 inhibitors such as fluoxetine, paroxetine, bupropion, and quinidine sharply raise levels and require dose reduction.
- CYP1A2 and CYP3A4 inducers including carbamazepine, rifampin, and tobacco smoke lower concentrations and can cause apparent nonresponse.
- Additive QT prolongation with methadone, ondansetron, and antiarrhythmics; additive anticholinergic burden with antihistamines and antispasmodics.
- Antagonizes the antihypertensive effect of clonidine and guanfacine, and potentiates sedation from alcohol, opioids, and benzodiazepines.

SPECIAL POPULATIONS

- Pregnancy data show no consistent teratogenic signal, though third-trimester exposure has been linked to transient neonatal withdrawal.
- Excreted into breast milk in small amounts; nortriptyline is generally chosen preferentially when a tricyclic is needed during lactation.
- Approved from age 6 years for enuresis only; antidepressant efficacy in pediatric depression has never been demonstrated in controlled trials.
- The Beers Criteria list imipramine as potentially inappropriate at age 65 and older because of anticholinergic and orthostatic burden.
- Use lower doses in hepatic impairment; no formal renal adjustment exists, but metabolites accumulate in advanced kidney disease.

☆ PRESCRIBING PEARLS

- Order the combined imipramine plus desipramine level, never the parent drug alone.
- Still the benchmark tricyclic for panic disorder, but start low since early jitteriness is common.
- The only TCA labeled for enuresis, capped at **2.5 mg/kg/day** in children.

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

Specgx LLC. (2023). *Tofranil (imipramine 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.