TRICYCLIC ANTIDEPRESSANT

Clomipramine

Anafranil

The most serotonergic tricyclic and the only one FDA-approved for obsessive-compulsive disorder, still the efficacy benchmark in refractory OCD.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
100-250 mg/day PO	32 h; desmethyl about 69 h	CYP2D6, CYP1A2, CYP3A4, 2C19	OCD 4-6 wks; 10-12 wks full

⚠ 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 obsessive-compulsive disorder in adults and in children and adolescents 10 years of age and older.
- Remains the efficacy benchmark in OCD meta-analyses, though selective serotonin reuptake inhibitors are preferred first line for tolerability.
- Off-label for depression in the United States, where it is approved as an antidepressant in many other countries but not by the FDA.
- Off-label for panic disorder, where controlled trials show efficacy at doses lower than those needed for obsessive-compulsive symptoms.
- Off-label for trichotillomania, body dysmorphic disorder, premature ejaculation, and cataplexy associated with narcolepsy.
- Reasonable next step after two failed adequate SSRI trials in OCD, either alone or combined with exposure and response prevention.

DOSING & TITRATION

- Start **25 mg PO daily** with food and titrate over the first 2 weeks toward **100 mg/day** in divided doses as tolerated.
- Adult maximum is **250 mg/day**; after titration the total dose may be consolidated at bedtime to limit daytime sedation.
- In children and adolescents 10 years and older the maximum is **3 mg/kg/day or 200 mg/day**, whichever amount is smaller.
- Supplied as 25, 50, and 75 mg capsules; adequate OCD trials require at least 10 to 12 weeks at the maximum tolerated dose.
- Reduce the dose in hepatic impairment and titrate slowly in renal impairment, since hydroxylated metabolites accumulate.
- Taper gradually over several weeks when stopping to avoid nausea, headache, malaise, insomnia, and cholinergic rebound symptoms.

MECHANISM OF ACTION

- The most potent serotonin reuptake inhibitor among tricyclics, with roughly tenfold greater affinity for the serotonin than norepinephrine transporter.
- Its major metabolite desmethylclomipramine is a strong norepinephrine reuptake inhibitor, so the drug is effectively dual-acting at steady state.
- Strong serotonergic tone in cortico-striato-thalamo-cortical circuits is the presumed basis of antiobsessional efficacy in OCD.
- Substantial muscarinic, histaminic, and alpha-1 blockade produces the anticholinergic effects, sedation, and orthostasis typical of the class.
- Dose-dependent lowering of seizure threshold is greater than for other tricyclics and is the main constraint on the maximum dose.

PHARMACOKINETICS

- Well absorbed orally, with bioavailability near 50 percent after extensive first-pass metabolism; take with food to reduce nausea.
- Parent drug half-life is about 32 hours while desmethylclomipramine averages roughly 69 hours, so steady state takes 1 to 2 weeks.
- Demethylation is mediated by CYP1A2, CYP3A4, and CYP2C19, and hydroxylation of both parent and metabolite proceeds through CYP2D6.
- CYP2D6 poor metabolizers and patients on strong 2D6 inhibitors accumulate drug substantially, warranting dose reduction and level checks.
- Highly protein bound with a large volume of distribution; renal excretion of conjugated metabolites accounts for most elimination.

ADVERSE EFFECTS

- Dry mouth affects roughly 84 percent, constipation about 47 percent, and somnolence about 54 percent of patients in registration trials.
- Sexual dysfunction is very common, with ejaculatory failure reported in about 42 percent of treated men in clinical trials.
- Seizures occur in approximately 0.5 percent at doses up to **250 mg/day** and rise steeply above that, making the ceiling a hard limit.
- Weight gain, tremor, sweating, and orthostatic dizziness are frequent and often drive discontinuation during long-term therapy.
- Cardiac conduction slowing with PR, QRS, and QT prolongation occurs at higher doses and dominates the picture in overdose.
- Rare serious events include hepatitis, agranulocytosis, syndrome of inappropriate antidiuretic hormone, and neuroleptic malignant-like reactions.

MONITORING

- Obtain a baseline ECG in patients over 50 years, in any known cardiac disease, and before exceeding **200 mg/day** in any adult.
- Plasma levels are not routinely required, but a combined clomipramine plus desmethylclomipramine level helps assess toxicity or nonresponse.
- Screen for seizure risk factors including head injury, alcohol withdrawal, and concurrent proconvulsant drugs before dose escalation.
- Track weight, blood pressure with orthostatics, and bowel function at each visit, and ask directly about sexual side effects.
- Use the Yale-Brown Obsessive Compulsive Scale at baseline and every 4 to 6 weeks to document response objectively.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of fatal serotonin syndrome risk.
- Strong CYP2D6 inhibitors including fluoxetine, paroxetine, and bupropion markedly raise levels and increase seizure and cardiac risk.
- CYP1A2 and CYP3A4 modulators matter: fluvoxamine and ketoconazole raise levels while carbamazepine and smoking lower them.
- Additive serotonergic burden with SSRIs, triptans, tramadol, and linezolid can precipitate serotonin syndrome even without an MAOI.
- Drugs that lower seizure threshold such as bupropion, tramadol, and high-dose antipsychotics compound the dose-dependent seizure risk.

SPECIAL POPULATIONS

- Pregnancy data are limited; third-trimester exposure has been associated with neonatal jitteriness, tremor, and feeding difficulty.
- Present in breast milk at low relative infant dose; monitor the infant for sedation and poor feeding if used during lactation.
- Approved from age 10 years for OCD, with weight-based capping and close monitoring for suicidality and cardiac effects required.
- Beers Criteria list tricyclics as potentially inappropriate at age 65 and older; if used, start at **10-25 mg** with slow titration.
- Lower doses are needed in hepatic impairment, and clearance of metabolites is reduced in significant chronic kidney disease.

PRESCRIBING PEARLS

- Adequate OCD trials need 10-12 weeks at the maximum tolerated dose before calling it a failure.
- Seizure risk is the ceiling: never exceed **250 mg/day** in adults.
- Ejaculatory failure occurs in about 4 of 10 men; ask directly or adherence quietly fails.

References

American Psychiatric Association. (2007). *Practice guideline for the treatment of patients with obsessive-compulsive disorder*. 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

Mallinckrodt Inc. (2023). *Anafranil (clomipramine hydrochloride) capsules [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

National Institute for Health and Care Excellence. (2005). *Obsessive-compulsive disorder and body dysmorphic disorder: Treatment* (Clinical Guideline CG31). https://www.nice.org.uk/guidance/cg31

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.