TRICYCLIC ANTIDEPRESSANT

Nortriptyline

Pamelor, Aventyl (brand discontinued in US)

Secondary-amine TCA, the best tolerated of the class, and the only antidepressant with a well established therapeutic plasma window.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
75-150 mg/day PO	18-44 h (mean about 36 h)	CYP2D6; 10-OH metabolite	2-4 wks; 6 wks for 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; endogenous depressions respond better than reactive presentations.
- Off-label but widely used for painful diabetic neuropathy, postherpetic neuralgia, and other chronic neuropathic pain conditions.
- Off-label for migraine and chronic tension-type headache prophylaxis, usually at 10-50 mg at bedtime rather than antidepressant doses.
- Off-label adjunct for smoking cessation, with efficacy comparable to bupropion in older trials but a less favorable side effect profile.
- Preferred tricyclic in older adults and in patients who could not tolerate amitriptyline, imipramine, or doxepin because of orthostasis.
- Not approved for pediatric patients; adolescent use is off-label and carries the antidepressant class suicidality warning.

DOSING & TITRATION

- Start **25 mg PO at bedtime** in adults, or **10 mg** in older patients, and increase by 25 mg every 3 to 7 days as tolerated.
- Usual antidepressant target is **75-150 mg/day**; the label states that total daily doses above **150 mg/day** are not recommended.
- For neuropathic pain and headache prophylaxis, **10-75 mg at bedtime** is usually sufficient and better tolerated than higher doses.
- Supplied as 10, 25, 50, and 75 mg capsules and a 10 mg per 5 mL oral solution; the full dose is customarily given at bedtime.
- No renal dose adjustment is specified, but reduce the dose in hepatic impairment and in patients with confirmed CYP2D6 poor metabolizer status.
- Taper gradually over 2 to 4 weeks when discontinuing to avoid cholinergic rebound with nausea, headache, insomnia, and malaise.

MECHANISM OF ACTION

- Predominantly blocks the norepinephrine transporter, with far weaker serotonin reuptake inhibition than tertiary amines such as amitriptyline.
- Muscarinic, histaminergic, and alpha-1 adrenergic blockade are all present but substantially weaker than with the tertiary-amine tricyclics.
- Reduced alpha-1 blockade translates into much less orthostatic hypotension, which is why it is the preferred tricyclic in geriatric practice.
- Sodium channel blockade underlies analgesia in neuropathic pain and also the cardiac conduction delay seen with toxic concentrations.
- Noradrenergic action in descending inhibitory pain pathways explains analgesic benefit at doses well below those needed for antidepressant effect.

PHARMACOKINETICS

- Well absorbed after oral dosing with peak concentrations at roughly 7 to 8.5 hours; the active metabolite of amitriptyline is this same molecule.
- Elimination half-life averages about 36 hours with a range of 18 to 44 hours, so once-daily bedtime dosing is adequate for most patients.
- Hydroxylated primarily by CYP2D6 to 10-hydroxynortriptyline, a metabolite with modest activity that accumulates in renal impairment.
- CYP2D6 poor metabolizers reach much higher concentrations; CPIC recommends a 50 percent dose reduction with level-guided titration in this group.
- Highly protein bound with a large volume of distribution, so extracorporeal removal is ineffective and overdose management is supportive.

ADVERSE EFFECTS

- Dry mouth, constipation, blurred vision, and urinary hesitancy are common but milder than with tertiary-amine tricyclics.
- Sedation and weight gain occur but are less pronounced than with amitriptyline or doxepin, aiding tolerability in long-term use.
- Orthostatic hypotension is the least of any tricyclic, yet it still occurs and remains a fall risk in frail older patients.
- Cardiac conduction delay with PR, QRS, and QTc prolongation is dose dependent and becomes dangerous above the therapeutic window.
- Overdose is potentially lethal with seizures, wide-complex arrhythmia, hypotension, and coma; dispense limited quantities in high-risk patients.
- Lowers the seizure threshold, can induce mania in bipolar illness, and rarely causes agranulocytosis or cholestatic liver injury.

MONITORING

- Nortriptyline has a true therapeutic window of **50-150 ng/mL**; levels above 150 ng/mL are associated with reduced response and greater toxicity.
- Draw the level as a trough 10 to 14 hours after the bedtime dose and at least 5 days after any dose change or steady state is not reached.
- Obtain a baseline ECG in patients over 50 years, in known cardiac disease, and repeat after reaching target dose or after any level above range.
- Check blood pressure with orthostatics, weight, and bowel and bladder function at each visit during titration and periodically thereafter.
- Monitor for emergent suicidality, agitation, and mood switch during the first weeks of therapy and after every 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 double or triple levels and demand a dose reduction.
- Inducers including carbamazepine, rifampin, and chronic smoking lower concentrations and may cause apparent treatment failure at usual doses.
- Additive QT prolongation occurs with methadone, ondansetron, and class IA or III antiarrhythmics; additive anticholinergic load with oxybutynin.
- Blunts the antihypertensive action of clonidine and guanfacine, and alcohol or sedatives potentiate central nervous system depression.

SPECIAL POPULATIONS

- Human pregnancy data are limited but do not show a clear teratogenic signal; late exposure can cause transient neonatal irritability.
- Relative infant dose in breast milk is low and levels in infants are usually undetectable, making this a preferred tricyclic during lactation.
- Pediatric safety and efficacy have not been established, and enuresis or pain indications in children are entirely off-label.
- Preferred tricyclic in adults 65 and older, though the Beers Criteria still flag the whole class; start at **10 mg** and use levels to guide dosing.
- The 10-hydroxy metabolite accumulates in renal impairment, so check levels sooner and titrate slowly in advanced kidney disease.

☆ PRESCRIBING PEARLS

- The only antidepressant with a real therapeutic window: **50-150 ng/mL**, with worse response above it.
- Draw the level as a trough 10-14 h post dose, at least 5 days after any change.
- Best tolerated tricyclic in older adults because alpha-1 blockade is comparatively weak.

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.