MONOAMINE OXIDASE INHIBITOR

Phenelzine

Nardil

Irreversible nonselective MAO inhibitor with strong efficacy in atypical and treatment-resistant depression, at the cost of diet restrictions.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
45-90 mg/day PO divided	11.6 h; MAO recovery 2 wks	Acetylation; MAO oxidation	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; phenelzine is not approved for use in pediatric patients.

INDICATIONS

- FDA-approved for adult patients with depression characterized as atypical, nonendogenous, or neurotic who have failed other therapy.
- The label positions it as a treatment for patients who have not responded to a trial of other antidepressant drug therapy.
- Off-label but well supported for treatment-resistant major depression, particularly with hypersomnia, hyperphagia, and rejection sensitivity.
- Off-label for social anxiety disorder, where controlled trials showed effect sizes larger than those achieved by SSRIs.
- Off-label for panic disorder and for posttraumatic stress disorder when first-line and second-line agents have failed.
- Not approved for pediatric use, and safety and efficacy in children and adolescents have never been established.

DOSING & TITRATION

- Start **15 mg PO three times daily**, then increase to at least **60 mg/day** fairly rapidly because lower doses often fail.
- Doses of **60-90 mg/day** are usually required for response; **90 mg/day** is the maximum recommended in the label.
- Allow up to 4 weeks at the target dose before declaring the trial a failure, and do not stop prematurely for early jitteriness alone.
- Once a sustained response is achieved, the dose may be reduced slowly to a maintenance level as low as **15 mg daily or every other day**.
- Supplied only as 15 mg tablets; the tyramine-restricted diet must start with the first dose and continue for 2 weeks after the last dose.
- Taper gradually when discontinuing, and observe a full **14-day washout** before starting any serotonergic or sympathomimetic agent.

MECHANISM OF ACTION

- Forms an irreversible covalent bond with both MAO-A and MAO-B, so activity returns only as new enzyme is synthesized over about 2 weeks.
- MAO-A inhibition raises synaptic serotonin, norepinephrine, and dopamine, producing broad monoaminergic enhancement not achievable with reuptake blockers.
- MAO-A inhibition in gut wall and liver removes first-pass degradation of dietary tyramine, which is the basis of the hypertensive crisis risk.
- Absorbed tyramine displaces norepinephrine from sympathetic nerve terminals, causing an abrupt pressor surge minutes to hours after ingestion.
- A hydrazine derivative that also inhibits several other enzymes and can deplete pyridoxine, explaining the paresthesias seen in some patients.

PHARMACOKINETICS

- Rapidly absorbed orally with peak plasma concentrations within 2 to 4 hours of an oral dose, and food does not meaningfully interfere.
- Plasma half-life is only about 11.6 hours, but this number is clinically irrelevant because enzyme inhibition is irreversible.
- Metabolized largely by acetylation and by oxidation, with phenylacetic acid and parahydroxyphenylacetic acid as principal metabolites.
- Slow acetylators may reach higher concentrations and experience more adverse effects at any given dose than rapid acetylators.
- Functional recovery of monoamine oxidase requires roughly 2 weeks after the last dose, which sets every washout interval for this drug.

ADVERSE EFFECTS

- Orthostatic hypotension is the most common dose-limiting effect and often appears paradoxically several weeks into treatment.
- Weight gain, peripheral edema, and daytime sedation are frequent, while insomnia and afternoon somnolence are also commonly reported.
- Sexual dysfunction including anorgasmia occurs in a large minority of patients and is a leading reason for discontinuation.
- Hypertensive crisis with occipital headache, stiff neck, palpitations, and photophobia follows dietary tyramine or sympathomimetic exposure.
- Serotonin syndrome with hyperthermia, rigidity, clonus, and autonomic instability can be fatal when serotonergic drugs are combined.
- Pyridoxine deficiency causing paresthesias, and rare hepatocellular injury characteristic of hydrazine drugs, are both described.

MONITORING

- Check supine and standing blood pressure at every visit, and teach the patient to monitor at home during the titration period.
- Give written tyramine diet instructions and confirm understanding before the first dose; the diet continues 2 weeks after stopping.
- Obtain baseline liver enzymes and repeat if malaise, jaundice, or anorexia develops, given the hydrazine hepatotoxicity signal.
- Ask about paresthesias at each visit and consider pyridoxine **50-100 mg daily** if they appear during long-term treatment.
- Review the complete medication list including over-the-counter cold remedies at every encounter, since new agents are the usual source of harm.

INTERACTIONS & CAUTIONS

- Absolutely contraindicated with SSRIs, SNRIs, tricyclics, triptans, tramadol, meperidine, linezolid, methylene blue, and St. John's wort.
- Contraindicated with sympathomimetics including pseudoephedrine, phenylephrine, amphetamines, and with dextromethorphan and buspirone.
- Requires a **14-day washout** in both directions with most antidepressants, and a **5-week washout** after stopping fluoxetine.
- Contraindicated in pheochromocytoma, congestive heart failure, hepatic disease, and with a history of frequent severe headache.
- Avoid meperidine entirely; morphine, fentanyl, and hydromorphone are safer opioid choices when analgesia cannot be avoided.

SPECIAL POPULATIONS

- Pregnancy data are sparse and animal studies suggest possible fetal harm; the tyramine and drug restrictions further complicate obstetric care.
- Lactation data are essentially absent, so an alternative antidepressant is preferred for a woman who intends to breastfeed.
- Not approved and not recommended in patients under 16 years of age, and dietary adherence is difficult to guarantee in adolescents.
- Older adults are especially vulnerable to orthostatic hypotension and falls; start at **15 mg daily** and titrate very cautiously.
- Contraindicated in significant hepatic impairment; use with caution and reduced doses in severe renal impairment.

PRESCRIBING PEARLS

- Underdosing is the usual cause of failure; most responders need **60-90 mg/day**.
- Diet and drug restrictions persist 2 weeks after the last dose because MAO must be resynthesized.
- Fluoxetine needs a **5-week washout** before starting an MAOI; 14 days is not enough.

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.