ATYPICAL ANTIDEPRESSANT

Mirtazapine

Remeron, Remeron SolTab

Sedating noradrenergic and specific serotonergic antidepressant that reliably restores sleep and appetite at the cost of weight gain.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
15-45 mg/day PO at bedtime	20-40 h	CYP2D6, 1A2, 3A4	Sleep night 1; mood 1-2 wks

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk of suicidality in pediatric and young adult patients in short-term studies. Closely monitor all treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Not approved for use in pediatric patients.

INDICATIONS

- FDA-approved only for major depressive disorder in adults, given once daily at bedtime in a range of **15 to 45 mg/day**.
- Off-label for insomnia in depression, where its antihistaminic sedation acts on the first night rather than after weeks.
- Off-label for appetite stimulation and weight gain in cancer cachexia, geriatric failure to thrive, and anorexia nervosa.
- Off-label as an augmentation agent added to an SSRI or SNRI, a combination whose additive efficacy is supported by several trials.
- Off-label for chemotherapy-induced and functional nausea, exploiting the same 5-HT3 antagonism that ondansetron uses.
- Off-label for PTSD-related nightmares and insomnia, though prazosin and trauma-focused psychotherapy remain better supported.

DOSING & TITRATION

- Start **15 mg** PO at bedtime; some clinicians begin at 7.5 mg when sedation is the main goal or the patient is frail.
- Increase at intervals of no less than one to two weeks toward the usual target of **30 mg/day**, with a maximum of **45 mg/day**.
- Sedation is often worse at 7.5 to 15 mg than at 30 mg, because noradrenergic activation increases relative to antihistaminic effect.
- Available as 7.5, 15, 30, and 45 mg tablets and as 15, 30, and 45 mg orally disintegrating tablets useful when swallowing is impaired.
- Reduce the dose and titrate slowly in renal or hepatic impairment, where clearance falls by 30 to 50 percent.
- Taper over two to four weeks when stopping, since abrupt cessation can produce nausea, dizziness, agitation, and rebound insomnia.

MECHANISM OF ACTION

- Blocks presynaptic alpha-2 autoreceptors and heteroreceptors, releasing the brake on both norepinephrine and serotonin release.
- Potent 5-HT2A, 5-HT2C, and 5-HT3 antagonism channels the increased serotonin toward 5-HT1A transmission rather than the other subtypes.
- Blocking 5-HT2A and 5-HT2C prevents the insomnia, agitation, and sexual dysfunction that follow unopposed serotonin reuptake inhibition.
- Blocking 5-HT3 prevents nausea and diarrhea, which is why mirtazapine is far better tolerated than SSRIs in the gut.
- Potent histamine H1 antagonism produces the sedation and appetite stimulation that dominate at low doses and lessen as the dose rises.

PHARMACOKINETICS

- Rapidly and completely absorbed with about 50 percent bioavailability after first-pass metabolism; food has minimal effect.
- Half-life is **20 to 40 hours** and is longer in women and older adults, comfortably supporting once-daily bedtime dosing.
- Metabolized by CYP2D6, CYP1A2, and CYP3A4, so no single enzyme dominates and interaction risk is only moderate.
- The demethyl metabolite is weakly active and contributes little; steady state is reached in about five days.
- Clearance falls by roughly 30 percent in moderate renal impairment, 50 percent in severe impairment, and about 30 percent in cirrhosis.

ADVERSE EFFECTS

- Somnolence occurs in over 50 percent of patients and is the leading reason for discontinuation, particularly at doses below 30 mg/day.
- Increased appetite affects about 17 percent and clinically meaningful weight gain about 12 percent, often several kilograms in the first year.
- Dry mouth, constipation, dizziness, and elevated cholesterol and triglycerides are common and warrant metabolic monitoring.
- Agranulocytosis or severe neutropenia occurred in roughly **1.1 per 1000** patients in premarketing trials, usually within the first two months.
- Sexual dysfunction and gastrointestinal upset are notably rare, which is the main reason to choose mirtazapine over an SSRI.
- QT prolongation and torsades de pointes have been reported, chiefly in overdose or with other QT-prolonging drugs.

MONITORING

- Obtain a complete blood count if fever, sore throat, stomatitis, or other signs of infection develop, and stop the drug pending results.
- Check weight at baseline and every one to three months, and obtain fasting lipids and glucose at baseline and annually.
- Assess suicidality, activation, and daytime sedation weekly for the first four weeks and after each dose change.
- Track sleep and appetite as early markers of effect, since both often improve within days while mood takes weeks.
- Obtain an ECG only in patients with cardiac disease or on other QT-prolonging medications, since routine ECG is not required.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Additive sedation with benzodiazepines, opioids, alcohol, and antihistamines is the most common clinically relevant interaction.
- Strong CYP3A4 inhibitors such as ketoconazole and ritonavir raise mirtazapine levels, while carbamazepine and rifampin lower them markedly.
- Serotonin syndrome is possible when combined with SSRIs, SNRIs, tramadol, or triptans, although 5-HT2 and 5-HT3 blockade lower the risk.
- Additive QT risk with methadone, antipsychotics, ondansetron, and class III antiarrhythmics warrants attention in medically complex patients.

SPECIAL POPULATIONS

- Pregnancy data are moderate and show no clear teratogenic signal, and its antiemetic action can help hyperemesis-associated depression.
- Relative infant dose in breast milk is under 2 percent, so mirtazapine is generally considered compatible with breastfeeding.
- Not approved in pediatrics, and a controlled pediatric depression trial failed to separate from placebo while producing weight gain.
- Often favored in frail older adults with insomnia, poor appetite, and weight loss, but falls and sedation must be weighed carefully.
- Reduce the dose in renal impairment, where clearance falls by 30 to 50 percent, and in cirrhosis, where it falls by about 30 percent.

PRESCRIBING PEARLS

- Lower doses are more sedating; raising to 30 mg often reduces daytime somnolence rather than worsening it.
- Best antidepressant when insomnia, nausea, and weight loss coexist with depression.
- Get a CBC for any fever or sore throat: agranulocytosis is rare but real, about 1 in 1000.

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.