SEROTONIN MODULATOR

Vortioxetine

Trintellix

Multimodal serotonergic antidepressant with a long half-life, dose-related nausea, and the best evidence for improving cognition in depression.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
10-20 mg/day PO	66 h	CYP2D6 major, 3A4/2C19 minor	1-2 wks; 6-8 wks full

⚠ 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 for major depressive disorder in adults, started at **10 mg once daily** and increased to 20 mg/day as tolerated.
- Not approved for any pediatric indication; adolescent depression trials did not consistently separate from placebo.
- Off-label for generalized anxiety disorder, where the trial results were mixed and did not support a US anxiety indication.
- Randomized trials show improvement in processing speed and executive function in depression that is partly independent of mood change.
- A reasonable off-label choice when residual cognitive complaints persist after mood symptoms have improved on another antidepressant.
- Sometimes selected off-label after SSRI-induced sexual dysfunction, since switching to vortioxetine improved sexual function in a comparative trial.

DOSING & TITRATION

- Start **10 mg** PO once daily with or without food; increase to **20 mg/day** as tolerated, since higher doses were more effective in trials.
- Use **5 mg/day** for patients who cannot tolerate 10 mg, and treat 20 mg/day as the maximum recommended dose.
- Halve the dose when a strong CYP2D6 inhibitor such as bupropion, fluoxetine, paroxetine, or quinidine is added.
- With a strong CYP inducer used beyond 14 days the dose may be increased, but not to more than three times the original dose.
- Available as 5, 10, and 20 mg film-coated tablets; there is no liquid or extended-release formulation.
- No adjustment is needed for renal impairment or mild to moderate hepatic impairment, and it is not recommended in severe hepatic impairment.

MECHANISM OF ACTION

- Inhibits the serotonin transporter while also acting directly at several serotonin receptor subtypes, which is why it is called multimodal.
- Antagonizes 5-HT3 and 5-HT7 receptors, actions linked in preclinical work to procognitive and antidepressant effects beyond reuptake blockade.
- Acts as a 5-HT1A agonist and 5-HT1B partial agonist, further increasing serotonergic tone and modulating raphe autoreceptor feedback.
- Downstream disinhibition of acetylcholine, norepinephrine, dopamine, and glutamate release is the proposed basis for its cognitive effects.
- 5-HT3 antagonism paradoxically coexists with high rates of nausea, which appears to be centrally rather than peripherally mediated.

PHARMACOKINETICS

- Bioavailability is about 75 percent and is unaffected by food, so it can be taken at any consistent time of day.
- Half-life is approximately **66 hours**, the longest among the newer antidepressants, so steady state takes about two weeks to reach.
- That long half-life makes discontinuation symptoms uncommon, though the label still advises reducing 15 to 20 mg doses to 10 mg for a week.
- Metabolized mainly by CYP2D6 with several minor enzymes contributing; the carboxylic acid metabolite is pharmacologically inactive.
- CYP2D6 poor metabolizers reach roughly twice the exposure of extensive metabolizers, which caps their dose at **10 mg/day**.

ADVERSE EFFECTS

- Nausea is the dominant adverse effect, rising from about 21 percent at 5 mg/day to roughly **32 percent at 20 mg/day** and more frequent in women.
- Nausea usually appears in the first week and resolves within two weeks; taking the dose with food and titrating slowly both help.
- Constipation, vomiting, dry mouth, dizziness, and abnormal dreams are the other common tolerability complaints.
- Sexual dysfunction is dose-related and appears lower than with SSRIs at 5 to 10 mg/day but approaches SSRI rates at 20 mg/day.
- Hyponatremia, serotonin syndrome, treatment-emergent mania, and increased bleeding with NSAIDs or anticoagulants are the serious risks.
- Weight change is minimal in short-term and one-year extension studies, an advantage over mirtazapine and paroxetine.

MONITORING

- Assess suicidality, activation, and agitation weekly for the first four weeks and after each dose change, especially in patients under 25.
- Ask specifically about nausea at week one and week two, since it peaks early and is the main driver of early discontinuation.
- Track mood with the PHQ-9 or MADRS every two to four weeks and consider a cognitive measure such as the DSST when cognition is the target.
- Check serum sodium at baseline and within two to four weeks in older adults and in patients on diuretics.
- Review the medication list for strong CYP2D6 inhibitors and for strong inducers whenever a new prescription is started.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP2D6 inhibitors, most commonly bupropion, fluoxetine, and paroxetine, double exposure and require halving the vortioxetine dose.
- Strong inducers such as rifampin, carbamazepine, and phenytoin can reduce exposure by more than half over two weeks of co-administration.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, lithium, tryptophan, and other serotonergic antidepressants.
- Increases bleeding risk with aspirin, NSAIDs, warfarin, and direct oral anticoagulants, as with the SSRIs.

SPECIAL POPULATIONS

- Pregnancy data are limited to registry and cohort reports without a clear teratogenic signal; better-studied agents are preferred if possible.
- Lactation data are sparse, so an antidepressant with established infant safety should generally be chosen when starting during breastfeeding.
- Not approved in pediatric patients, and the two adolescent depression trials did not establish efficacy over placebo.
- No dose adjustment is required by age, although older adults face greater hyponatremia and falls risk and may prefer 5 to 10 mg/day.
- No adjustment is needed in any degree of renal impairment, and severe hepatic impairment remains unstudied and not recommended.

PRESCRIBING PEARLS

- Nausea is dose-related and peaks in week one; start at 10 mg and take it with food.
- Best antidepressant evidence for improving processing speed independent of mood improvement.
- Halve the dose if bupropion, fluoxetine, or paroxetine is added, since all are strong 2D6 inhibitors.

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.