SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Sertraline

Zoloft

Broad-spectrum first-line SSRI with the widest anxiety labeling, low interaction burden, and the best safety data in pregnancy and lactation.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
50-200 mg/day PO	26 h; metabolite 62-104 h	CYP2B6, 2C19; weak 2D6 inhibitor	1-2 wks; 6-8 wks full

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk of suicidality in children, adolescents, and young adults in short-term studies, with no increase beyond age 24 and reduced risk at 65 and older. Monitor all patients closely for clinical worsening and emergent suicidal thoughts.

INDICATIONS

- FDA-approved for major depressive disorder in adults, typically at **50-200 mg/day**, with efficacy comparable to other first-line antidepressants.
- FDA-approved for obsessive-compulsive disorder in adults and in children from age 6, where doses at the top of the range are usually needed.
- FDA-approved for panic disorder, post-traumatic stress disorder, and social anxiety disorder, all started at **25 mg/day** to limit early activation.
- FDA-approved for premenstrual dysphoric disorder using either continuous daily dosing or luteal-phase-only dosing each cycle.
- Off-label for generalized anxiety disorder, binge-eating disorder, and premature ejaculation, with generalized anxiety the most common use.
- Frequently chosen off-label for depression or anxiety in pregnancy, in lactation, and in cardiac disease because of its reassuring safety record.

DOSING & TITRATION

- Start **50 mg** PO daily for depression or OCD; start **25 mg** daily for panic disorder, PTSD, or social anxiety, then raise after one week.
- Titrate by 25 to 50 mg no more often than weekly; usual effective range is 50 to 200 mg/day and the label maximum is **200 mg/day**.
- Pediatric OCD starts at **25 mg/day** in ages 6 to 12 and **50 mg/day** in ages 13 to 17, with the same 200 mg/day adult ceiling.
- Available as 25, 50, and 100 mg tablets, a 20 mg/mL oral concentrate that must be diluted before use, and 150 and 200 mg capsules.
- No renal adjustment is required; in mild hepatic impairment use a lower dose or longer interval, and avoid in moderate to severe impairment.
- Taper over two to four weeks when stopping, since abrupt withdrawal produces dizziness, paresthesia, irritability, and flu-like symptoms.

MECHANISM OF ACTION

- Blocks the presynaptic serotonin transporter with high potency and selectivity, increasing synaptic 5-HT throughout cortical and limbic circuits.
- Downstream desensitization of 5-HT1A somatodendritic autoreceptors restores raphe firing and underlies the delayed onset of antidepressant effect.
- Has modest dopamine transporter affinity, weak among clinical effects but possibly contributing to its slightly activating quality at higher doses.
- Binds sigma-1 receptors, an action of uncertain clinical meaning that has driven research interest in psychosis and in antiviral repurposing.
- Essentially devoid of muscarinic, histaminic, and alpha-adrenergic blockade, so anticholinergic load and orthostasis are minimal.

PHARMACOKINETICS

- Oral absorption is slow, with peak levels at 4 to 6 hours; food raises exposure modestly, so consistent dosing with or without meals is advised.
- Half-life averages **26 hours**, supporting once-daily dosing, and steady state is reached in about one week in most adults.
- Metabolized mainly by CYP2B6 with contributions from 2C19, 2C9, 3A4, and 2D6, so no single enzyme dominates and interaction risk stays low.
- N-desmethylsertraline has a 62 to 104 hour half-life but is 10 to 20 times less potent, contributing little to clinical effect.
- Only a weak to moderate CYP2D6 inhibitor below 150 mg/day, though inhibition becomes clinically relevant near the **200 mg/day** ceiling.

ADVERSE EFFECTS

- Diarrhea and loose stools occur in about 20 percent and are more frequent with sertraline than with any other SSRI, often improving over weeks.
- Nausea, insomnia, somnolence, tremor, headache, and diaphoresis are common early and generally settle within the first two weeks of treatment.
- Sexual dysfunction affects roughly **30-50 percent** of patients, including delayed orgasm, reduced libido, and erectile difficulty.
- Hyponatremia from SIADH, increased bleeding with NSAIDs or anticoagulants, and bruxism are the notable non-serotonergic safety issues.
- Serotonin syndrome, treatment-emergent mania in undiagnosed bipolar disorder, and rare akathisia are the serious effects that change prescribing.
- Modest weight gain of 1 to 2 kg is typical over a year of treatment, less than with paroxetine or mirtazapine.

MONITORING

- Reassess suicidality, activation, and agitation weekly for four weeks and after each dose increase, with the closest attention under age 25.
- Check sodium at baseline and within two to four weeks in older adults, diuretic users, or anyone developing confusion, falls, or lethargy.
- Use PHQ-9, GAD-7, PCL-5, or Y-BOCS at baseline and every two to four weeks to guide titration rather than global impression.
- No routine ECG, plasma levels, or laboratory monitoring is required in otherwise healthy adults taking sertraline alone.
- Screen for bipolar disorder before starting and recheck sleep, energy, and impulsivity if response looks unusually rapid or excessive.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** either side, and with pimozide because of additive QT prolongation and raised pimozide levels.
- The oral concentrate contains alcohol and is contraindicated in patients taking disulfiram; the tablets carry no such restriction.
- Additive serotonin syndrome risk with triptans, tramadol, linezolid, methylene blue, fentanyl, and St. John's wort.
- Inhibits CYP2D6 meaningfully only near **200 mg/day**, when tricyclic, metoprolol, and atomoxetine levels may rise and warrant reassessment.
- Increases bleeding risk with aspirin, NSAIDs, and anticoagulants, and modestly raises warfarin INR, so recheck INR after any dose change.

SPECIAL POPULATIONS

- Among the best-studied antidepressants in pregnancy, with no consistent teratogenic signal and low placental transfer relative to other SSRIs.
- Preferred SSRI in lactation because relative infant dose is under 2 percent and infant serum levels are usually undetectable.
- Approved from age 6 for OCD; pediatric depression use is off-label and requires close monitoring for activation and suicidality.
- In older adults start at **25 mg/day** given hyponatremia, falls, and bleeding risk, but sertraline remains a preferred geriatric SSRI.
- No dose change is needed in renal impairment, including dialysis, because clearance is almost entirely hepatic.

PRESCRIBING PEARLS

- Diarrhea is the signature early side effect; take with food and it usually resolves in two weeks.
- Preferred SSRI in pregnancy and breastfeeding, and the safest choice after myocardial infarction.
- 2D6 inhibition only matters near 200 mg/day, so it is easy to combine with other psychotropics.

References

Bousman, C. A., Stevenson, J. M., Ramsey, L. B., Sangkuhl, K., Hicks, J. K., Strawn, J. R., Singh, A. B., Ruano, G., Mueller, D. J., Tsermpini, E. E., Brown, J. T., Bell, G. C., Leeder, J. S., Gaedigk, A., Scott, S. A., Klein, T. E., Caudle, K. E., & Bishop, J. R. (2023). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants. *Clinical Pharmacology & Therapeutics*, *114*(1), 51-68. https://doi.org/10.1002/cpt.2903

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

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., & Van Ameringen, M. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, *14*(Suppl. 1), S1. https://doi.org/10.1186/1471-244X-14-S1-S1

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A. J., MacQueen, G. M., McInerney, S. J., McIntosh, D., Milev, R. V., Muller, D. J., Parikh, S. V., Pearson, N. L., Ravindran, A. V., & Uher, R. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *The Canadian Journal of Psychiatry*, *61*(9), 540-560. https://doi.org/10.1177/0706743716659417

National Library of Medicine. (2024). *Sertraline*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a697048.html

Pfizer. (2024). *Zoloft (sertraline hydrochloride) [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

U.S. Department of Veterans Affairs & U.S. Department of Defense. (2022). *VA/DoD clinical practice guideline for the management of major depressive disorder*. https://www.healthquality.va.gov/guidelines/MH/mdd/

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.