SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Fluoxetine

Prozac, Prozac Weekly, Sarafem, Symbyax (with olanzapine)

Long-half-life SSRI, first-line for depression and anxiety, and the only SSRI approved for pediatric major depressive disorder.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
20-80 mg/day PO	1-4 d; norfluoxetine 4-16 d	CYP2D6/2C9; strong 2D6 inhibitor	1-2 wks; 6-8 wks full

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased risk in children, adolescents, and young adults in short-term studies, with no increase after age 24 and reduced risk at 65 and older. Monitor all patients closely for clinical worsening and emergent suicidality. Not approved under age 7.

INDICATIONS

- FDA-approved for major depressive disorder in adults and in children and adolescents aged 8 years and older, usually at **20-60 mg/day**.
- FDA-approved for obsessive-compulsive disorder from age 7, for bulimia nervosa in adults at **60 mg/day**, and for panic disorder.
- FDA-approved in combination with olanzapine for acute bipolar I depression and for treatment-resistant unipolar depression in adults.
- FDA-approved as Sarafem for premenstrual dysphoric disorder, given continuously or only during the luteal phase at **20 mg/day**.
- Off-label for social anxiety disorder, generalized anxiety disorder, PTSD, binge-eating disorder, and selective mutism in children.
- Off-label for body dysmorphic disorder and trichotillomania, both of which usually require doses in the higher OCD range.

DOSING & TITRATION

- Start **20 mg** PO each morning for depression, OCD, or PMDD; in panic disorder begin at **10 mg/day** for one week to limit early jitteriness.
- Titrate by 10 to 20 mg increments no more often than every one to two weeks; usual target is **20-60 mg/day** and the label maximum is **80 mg/day**.
- Bulimia nervosa is dosed directly at **60 mg/day**, and OCD commonly needs 40 to 80 mg/day before response is judged inadequate.
- Formulations include 10, 20, and 40 mg capsules, 10 and 20 mg tablets, 20 mg per 5 mL solution, and a 90 mg delayed-release weekly capsule.
- Pediatric dosing starts at **10 mg/day** with a target near 20 mg/day; lower-weight children are often maintained at 10 mg/day long term.
- No taper is needed at discontinuation given the long half-life, but reduce dose or use alternate-day dosing in cirrhosis.

MECHANISM OF ACTION

- Potently and selectively blocks the presynaptic serotonin transporter, raising synaptic 5-HT and progressively desensitizing 5-HT1A autoreceptors.
- That slow autoreceptor desensitization is why mood response lags two to six weeks behind the immediate transporter blockade seen on day one.
- Weak 5-HT2C antagonism disinhibits frontal norepinephrine and dopamine release, giving fluoxetine its activating and sometimes anxiogenic early profile.
- Negligible muscarinic, histaminic, and alpha-1 affinity, so it avoids the anticholinergic, sedating, and hypotensive burden of tricyclic antidepressants.
- Potent CYP2D6 inhibition is a property of this molecule rather than a class effect and drives most of its clinically important drug interactions.

PHARMACOKINETICS

- Well absorbed orally with bioavailability above 60 percent; food delays but does not reduce absorption, so it may be taken with or without meals.
- Half-life is **1 to 4 days** for the parent drug and **4 to 16 days** for the equipotent active metabolite norfluoxetine, the longest of any SSRI.
- Steady state requires four to five weeks and complete washout takes five to six weeks, which is what governs MAOI switching intervals.
- Metabolized by CYP2D6 and CYP2C9; kinetics are nonlinear above **20 mg/day** because the drug inhibits its own clearance as concentrations rise.
- About 94 percent protein bound, extensively distributed to tissue, and eliminated renally as inactive conjugates after hepatic demethylation.

ADVERSE EFFECTS

- Nausea in roughly 20 percent, headache, insomnia in 10 to 20 percent, nervousness, tremor, and anorexia are the usual early complaints.
- Sexual dysfunction affects **30-70 percent** of treated patients, is the leading cause of nonadherence, and seldom remits with continued exposure.
- More activating than other SSRIs, with early appetite suppression and modest weight loss; long-term weight change is close to neutral.
- Hyponatremia from SIADH occurs mainly in older adults on diuretics and may present as confusion, falls, or seizure within weeks of starting.
- Serotonin syndrome, increased bleeding with NSAIDs or antiplatelets, bruxism, and treatment-emergent mania are the events that change prescribing.
- Rash or urticaria occurs in about 7 percent; the label directs discontinuation if rash is accompanied by systemic features.

MONITORING

- Assess suicidality, activation, and mood switch weekly for the first four weeks and after every dose change, especially in patients under 25.
- Check serum sodium at baseline and again within two to four weeks in older adults, diuretic users, or anyone with new confusion or lethargy.
- Track response with PHQ-9, GAD-7, or Y-BOCS at baseline and every two to four weeks rather than relying on global clinical impression.
- Routine ECG and plasma levels are not required; obtain an ECG only with known long QT or concurrent QT-prolonging medication.
- Screen for bipolar disorder before starting and reassess if sleep need, energy, or goal-directed activity change abruptly during treatment.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one; after stopping fluoxetine wait **5 weeks** before any MAOI or linezolid course.
- Contraindicated with pimozide and thioridazine, since CYP2D6 inhibition raises their concentrations and causes dangerous QT prolongation.
- Strong CYP2D6 inhibition roughly doubles aripiprazole, risperidone, atomoxetine, metoprolol, and tricyclic levels and blocks tamoxifen activation.
- Additive serotonergic risk with triptans, tramadol, linezolid, methylene blue, and St. John's wort; watch for clonus, rigidity, and hyperthermia.
- Raises bleeding risk with NSAIDs, aspirin, and anticoagulants, and increases phenytoin and carbamazepine levels through CYP2C9 inhibition.

SPECIAL POPULATIONS

- Human data show no clear teratogenic signal; third-trimester exposure carries small risks of neonatal adaptation syndrome and persistent pulmonary hypertension.
- Relative infant dose in breast milk is higher than for sertraline, so sertraline is generally preferred when starting an SSRI de novo while nursing.
- Approved from age 8 for depression and age 7 for OCD, and it has the strongest pediatric efficacy evidence of any antidepressant.
- In older adults start at **10 mg/day** because of hyponatremia, falls, and bleeding risk, and account for the long half-life before adding interacting drugs.
- No adjustment is needed in renal impairment; in hepatic impairment lower the dose or extend the dosing interval to every other day.

PRESCRIBING PEARLS

- Longest half-life of any SSRI: little discontinuation syndrome, but a 5-week washout before any MAOI.
- Most activating SSRI. Dose in the morning and start at 10 mg in panic disorder.
- Strong 2D6 inhibitor: recheck aripiprazole, atomoxetine, metoprolol, tamoxifen, and codeine.

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.