SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Paroxetine

Paxil, Paxil CR, Pexeva, Brisdelle

Most potent and most sedating SSRI, broadly effective in anxiety but burdened by weight gain, potent CYP2D6 inhibition, and harsh discontinuation.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
20-50 mg/day PO (IR)	21 h; no active metabolite	CYP2D6; potent 2D6 inhibitor	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 antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Not approved for use in pediatric patients.

INDICATIONS

- FDA-approved in adults for major depressive disorder at **20-50 mg/day** of the immediate-release tablet, dosed once daily in the morning.
- FDA-approved for obsessive-compulsive disorder and panic disorder, both of which are usually titrated toward the **60 mg/day** ceiling.
- FDA-approved for social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder, making its anxiety labeling the broadest.
- Paroxetine CR is approved for major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder.
- Brisdelle, a **7.5 mg** paroxetine mesylate capsule, is approved for moderate to severe vasomotor symptoms of menopause, not for depression.
- Off-label for premature ejaculation and for hot flashes in breast cancer survivors, though tamoxifen users should receive a different agent.

DOSING & TITRATION

- Start **20 mg** PO daily in the morning for depression, social anxiety, generalized anxiety, or PTSD; use **10 mg/day** to start in panic disorder.
- Titrate by 10 mg no more often than weekly; maximum is **50 mg/day** for depression, generalized anxiety, and PTSD, and **60 mg/day** for OCD and panic.
- Controlled-release starts at 25 mg/day for depression with a 62.5 mg/day maximum, and at 12.5 mg/day for panic with a **75 mg/day** maximum.
- In severe renal or hepatic impairment and in older adults, start at **10 mg/day** and do not exceed 40 mg/day of the immediate-release form.
- Formulations include 10, 20, 30, and 40 mg tablets, 10 mg/5 mL suspension, 12.5, 25, and 37.5 mg CR tablets, and 7.5 mg mesylate capsules.
- Taper very slowly, often by 10 mg monthly with a liquid formulation at the end, because withdrawal is the most severe in the SSRI class.

MECHANISM OF ACTION

- The most potent serotonin transporter inhibitor of the marketed SSRIs, producing near-complete transporter occupancy at standard clinical doses.
- Weak norepinephrine transporter inhibition emerges at higher doses and may add antidepressant effect while worsening sweating and insomnia.
- Meaningful muscarinic antagonism gives it the anticholinergic profile of dry mouth, constipation, blurred vision, and cognitive dulling in elders.
- Nitric oxide synthase inhibition contributes to sexual dysfunction rates that are the highest reported among the SSRI class.
- Potent mechanism-based CYP2D6 inhibition is essentially irreversible, so its interaction effect persists for days after the drug is stopped.

PHARMACOKINETICS

- Completely absorbed with extensive first-pass metabolism; food has no clinically meaningful effect on the extent of absorption.
- Half-life is about **21 hours** with no active metabolites, which is why missed doses so reliably produce discontinuation symptoms.
- Metabolized almost entirely by CYP2D6, an enzyme it saturates and inactivates, producing markedly nonlinear dose-concentration relationships.
- Because of that autoinhibition, raising the dose from 20 to 40 mg/day can more than double plasma concentrations rather than simply doubling them.
- Poor CYP2D6 metabolizers and patients on fluoxetine or bupropion reach substantially higher exposures at any given prescribed dose.

ADVERSE EFFECTS

- Somnolence, fatigue, dry mouth, and constipation are more common than with other SSRIs and reflect its antimuscarinic and antihistaminic load.
- Weight gain averages 2 to 4 kg over a year, the highest among SSRIs, and is a frequent reason patients ask to switch agents.
- Sexual dysfunction occurs in **60-70 percent** of treated patients, with delayed or absent orgasm the most commonly reported complaint.
- Discontinuation syndrome with dizziness, electric-shock sensations, irritability, and vivid dreams begins within one to two days of a missed dose.
- Hyponatremia, increased bleeding with NSAIDs or anticoagulants, serotonin syndrome, and treatment-emergent mania are the serious concerns.
- First-trimester exposure has been linked to a small excess of cardiac septal defects, which changes prescribing in women of childbearing potential.

MONITORING

- Monitor suicidality, activation, and agitation weekly for the first four weeks and after each dose change, most closely in patients under 25.
- Confirm contraception plans or pregnancy status before starting in reproductive-age patients given the fetal cardiac signal.
- Check sodium at baseline and within two to four weeks in older adults and diuretic users, and whenever confusion or falls emerge.
- Track weight and waist circumference at baseline and every three months, since weight gain accumulates gradually and drives discontinuation.
- Review the full medication list for CYP2D6 substrates at every visit rather than only at initiation, since inhibition is durable.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs, linezolid, methylene blue, pimozide, and thioridazine, the latter two because of QT prolongation risk.
- Potent CYP2D6 inhibition roughly halves tamoxifen conversion to endoxifen, so avoid it entirely in patients taking tamoxifen for breast cancer.
- Raises levels of tricyclics, metoprolol, atomoxetine, risperidone, and aripiprazole, and blocks the analgesic activation of codeine and tramadol.
- Additive serotonergic risk with triptans, tramadol, fentanyl, and St. John's wort; additive anticholinergic burden with antihistamines and oxybutynin.
- Increases bleeding risk with aspirin, NSAIDs, and warfarin, and its own levels fall substantially with phenytoin, carbamazepine, or rifampin.

SPECIAL POPULATIONS

- Generally avoided in pregnancy, especially the first trimester, because of the association with cardiac septal defects reported in several cohorts.
- Compatible with breastfeeding at low relative infant doses, but sertraline remains the usual first choice when starting during lactation.
- Not approved in pediatric patients, and pediatric trials showed both poor efficacy in depression and elevated suicidality signals.
- In older adults limit to **40 mg/day** and expect anticholinergic cognitive effects, falls, and hyponatremia at a higher rate than with sertraline.
- Start at **10 mg/day** with a 40 mg/day ceiling in severe renal impairment with creatinine clearance under 30 mL/min or in severe hepatic impairment.

☆ PRESCRIBING PEARLS

- Worst discontinuation syndrome of any SSRI: never stop abruptly, and taper with liquid at the end.
- Never combine with tamoxifen; 2D6 inhibition blocks conversion to active endoxifen.
- Most sedating, most weight gain, most anticholinergic, and most sexual dysfunction of the SSRIs.

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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.