Medications for depression

First-line and second-line antidepressants, augmentation, treatment-resistant options, and the decision points that shape the pick. Reviewed against current guidelines as of June 8, 2026.

For most people starting treatment, an SSRI is the default. The runners-up are the SNRIs, bupropion, and mirtazapine. Any of them has decent odds of working. The choice usually turns on side effects, comorbidities, and what the patient will actually take. Companion to the full guide at psychiatryrx.org/guides/medications-for-depression/.

First-line options

Drug	Class	Notes
Sertraline	SSRI	Common default. Broad anxiety approvals. Wide dose range, cheap generic.
Escitalopram	SSRI	Often the most tolerable SSRI. Simple dosing. Cap 10 mg over 65 or with liver disease.
Fluoxetine	SSRI	Long half-life is forgiving of missed doses. Activating early. Cleanest to stop.
Paroxetine	SSRI	Works, but most sedating, most weight gain, hardest discontinuation. Rarely first pick now.
Citalopram	SSRI	Fine, though QT cap (40 mg most adults, 20 mg over 60) limits headroom.
Venlafaxine XR	SNRI	Depression plus anxiety. NE effect above 150 mg. Watch BP.
Duloxetine	SNRI	Best pick when depression comes with chronic pain, neuropathy, or fibromyalgia.
Bupropion	Atypical (NDRI)	No sexual side effects, no weight gain, activating. Also covers smoking cessation. Avoid in eating disorders and seizure risk.
Mirtazapine	Atypical (NaSSA)	Sedating, appetite-stimulating. Useful when insomnia and poor appetite are prominent.

Second-line and augmentation

Drug	Class	When to consider
Vortioxetine	Multimodal serotonergic	Partial response with sexual side effects or cognitive complaints.
Vilazodone	SSRI plus 5-HT1A partial agonist	Sexual side effect concern. Requires food for absorption.
Nortriptyline, desipramine	TCA	Treatment-resistant depression, or when neuropathic pain overlaps. Check baseline ECG.
Aripiprazole, brexpiprazole, cariprazine	Atypical antipsychotic augmentation	Partial response to an antidepressant at adequate dose and duration. Aripiprazole 2 to 15 mg, brexpiprazole 1 to 3 mg, cariprazine 1.5 to 3 mg.
Quetiapine XR	Atypical antipsychotic augmentation	FDA-approved augmentation at 150 to 300 mg. Heavily sedating.
Lithium	Augmentation	Underused. Adds antidepressant effect and reduces suicide risk. Target 0.4 to 0.8 mEq/L.

Liothyronine (T3)	Augmentation	STAR*D showed comparable to lithium at step 3, often better tolerated. 25 to 50 mcg.
Esketamine (Spravato)	NMDA antagonist	Treatment-resistant depression, and depression with suicidal ideation. Onset in days. REMS setting.
Dextromethorphan-bupropion (Auvelity)	NMDA antagonist plus NDRI	Faster onset than standard antidepressants in trials.
Phenelzine, tranylcypromine, selegiline patch	MAOI	Refractory or atypical depression. Diet and interaction rules apply.

Special considerations

- Pregnancy: sertraline is the most-studied SSRI. Avoid paroxetine in the first trimester. Untreated depression carries its own risks, so continuation is often the right call.
- Postpartum: brexanolone IV (60-hour infusion) and zuranolone (oral 14-day course) are approved for postpartum depression with onset in days.
- Older adults: sertraline, escitalopram, or mirtazapine are the workhorses. Avoid TCAs and paroxetine (Beers). Start low, go slow, but go. Watch for SIADH and orthostasis.
- Bipolar depression: SSRI monotherapy can trigger mania or accelerate cycling. Screen for a bipolar history before starting. If bipolar depression is confirmed, the algorithm changes.
- Comorbidity tips selection: pain (duloxetine), insomnia (mirtazapine), sexual side effect concern (bupropion, vortioxetine, vilazodone), fatigue (bupropion or NE-active SNRI dose), smoker (bupropion).

What tips the choice

Starting fresh with no strong comorbidity signal, sertraline or escitalopram is the default. Anxiety prominent, favor sertraline. Fatigue and low energy front and center, consider bupropion or an SNRI at NE-active doses. Insomnia and low appetite, mirtazapine can cover both. Sexual side effect concern from the start, bupropion or vortioxetine. Chronic pain overlap, duloxetine. Poor adherence pattern, fluoxetine's long half-life is forgiving. Family history of good response to a specific drug, reasonable to lean that way.

Watchouts

- Boxed warning: possible increase in suicidal thoughts in people under 25, especially early or after dose changes.
- Don't treat suspected bipolar depression with SSRI monotherapy. Screen for prior manic or hypomanic episodes.
- Serotonin syndrome risk with combinations: tramadol, triptans, dextromethorphan, lithium, St John's wort.
- Bleeding risk on SSRIs plus NSAIDs, aspirin, or anticoagulants. Consider a stomach-protecting step.
- Hyponatremia is more common in older adults, especially the first weeks. Check sodium if lethargy or confusion appear.
- Never stop paroxetine or venlafaxine abruptly. Discontinuation is real. Plan a taper.
- MAOI washout: about 5 weeks after fluoxetine, 2 weeks after most other antidepressants.

Reviewed against current guidelines as of June 8, 2026. Educational reference, not medical advice.