Comorbidity medication selection

The primary diagnosis picks the class. The comorbidity picks the drug within the class. Reviewed against current guidelines as of June 8, 2026.

For most psychiatric conditions, three or four options within a class have comparable efficacy. Side effect profiles and secondary indications diverge sharply. When a patient has depression plus something else, that something-else is usually the deciding factor. The table below is not exhaustive. It's the pairs that come up over and over in outpatient practice.

The comorbidity matrix

Comorbidity pair	First-line	Second-line	Avoid or use caution	Rationale
MDD + insomnia	Mirtazapine, trazodone adjunct	Doxepin 3 to 6 mg	Fluoxetine at bedtime, bupropion at bedtime	Histaminergic and serotonergic sedation
MDD + sexual concern	Bupropion, vortioxetine	Vilazodone, mirtazapine	SSRIs (especially paroxetine), SNRIs	Avoid strong serotonergic reuptake blockade
MDD + weight concern	Bupropion, vortioxetine	Escitalopram	Mirtazapine, paroxetine, TCAs	Metabolic profile
MDD + anxiety	Sertraline, escitalopram, mirtazapine	Duloxetine, venlafaxine	Bupropion monotherapy	Serotonergic anxiolytic effect
MDD + fatigue	Bupropion, sertraline mid-dose, SNRI	Adjunctive stimulant with caution	Mirtazapine, paroxetine	Noradrenergic and dopaminergic activation
MDD + ADHD	Bupropion; SSRI plus stimulant	Atomoxetine plus SSRI	Fluoxetine or paroxetine with atomoxetine (2D6)	Dual coverage or compatible combination
MDD + chronic pain	Duloxetine, venlafaxine (over 150 mg)	Amitriptyline low-dose	TCAs in older adults (anticholinergic)	Descending inhibition via SNRI
MDD + migraine	Venlafaxine, amitriptyline	Nortriptyline	MAOIs (triptan interactions)	Preventive effect at low doses
MDD + hot flashes	Venlafaxine, escitalopram	Paroxetine (avoid in tamoxifen), gabapentin	Paroxetine in tamoxifen users	SNRI vasomotor effect
MDD + smoking	Bupropion	Bupropion plus varenicline		Dual FDA-approved indication
Bipolar + anxiety	Lamotrigine plus benzo bridge, quetiapine	Lurasidone	Antidepressant monotherapy	Mood-stabilizing base
Bipolar + insomnia	Quetiapine low-dose	Gabapentin, ramelteon	Chronic benzos, Z-drugs	Non-destabilizing sedation
Bipolar + ADHD	Stabilize mood, then stimulant carefully; or guanfacine	Atomoxetine	Stimulant monotherapy	Switch risk without mood stabilizer

Psychosis + PTSD	Quetiapine, risperidone; prazosin adjunct	Olanzapine		Nightmare and sleep coverage
Psychosis + substance use	LAI aripiprazole	LAI risperidone or paliperidone		Adherence support
Treatment-resistant psychosis	Clozapine	Clozapine augmentation		Unique efficacy
Panic + substance use	SSRI (sertraline, escitalopram)	Gabapentin adjunct	Chronic benzodiazepines	Non-reinforcing profile
OCD + depression	High-dose SSRI	Clomipramine	Suboptimal SSRI dosing	OCD needs higher receptor coverage
GAD + depression	SSRI or SNRI	Buspirone adjunct		Dual coverage
ADHD + anxiety	SSRI plus stimulant; or atomoxetine, guanfacine		Stimulant monotherapy if anxiety prominent	Cover both axes
ADHD + tics	Guanfacine, atomoxetine	Stimulants with monitoring		Tic modulation profile

Three principles

- The comorbidity picks the drug within the class. Efficacy inside a class is broadly comparable; side effect profile and secondary indications aren't.
- Bupropion is the workhorse when weight, sexual side effects, fatigue, ADHD, or smoking are on the table. Avoid as monotherapy when anxiety is dominant.
- Duloxetine covers depression plus chronic pain, fibromyalgia, or diabetic neuropathy in one drug. Venlafaxine over 150 mg is the second pick for the same pattern.
- In bipolar, mood stabilizer is the foundation. Antidepressant monotherapy in bipolar I is generally considered contraindicated. If you use an antidepressant, an SSRI with a mood stabilizer, monitor for switch, and be willing to stop it.
- For psychosis with active substance use, LAI aripiprazole solves adherence and metabolic burden simultaneously.

Not medical advice.