

PSYCHOPHARMACOLOGY

CLINICAL PEARLS



SCHIZOPHRENIA

- **All non-clozapine antipsychotics have roughly equivalent efficacy**; selection should be driven by side-effect profile, formulation, and prior response. Slight efficacy advantages have been suggested for clozapine, amisulpride, olanzapine, and risperidone in meta-analyses. [1-4]
- Antipsychotics are effective when **~70% of D2 receptors are occupied**, corresponding to mid-range doses. Pushing doses higher increases side effects without improving efficacy. The optimal maintenance dose is approximately **5 mg/day risperidone equivalents**; for patients in remission, doses as low as 2.5 mg/day may suffice. [1][5]
- **First-episode patients** respond to lower doses and have higher response rates than multi-episode patients — start low. [1]
- There is a **lag of ~2 weeks** before broad psychotic symptom improvement; avoid premature dose escalation in the first days to weeks. [1]
- **Clozapine** should be reserved for treatment-resistant psychosis (failure of ≥ 2 adequate antipsychotic trials of ≥ 6 weeks). It has superior efficacy for positive symptoms but requires REMS monitoring for agranulocytosis. [6]
- **Long-acting injectables (LAIs)** improve adherence and should be considered early, not just as a last resort. Once-daily nighttime dosing is another practical adherence strategy. [3]
- Avoid antipsychotic polypharmacy — switch rather than augment when the first agent fails. [2]

Metabolic Monitoring — All Atypical Antipsychotics

Metabolic syndrome is the most clinically impactful long-term adverse effect. The highest-risk agents are **clozapine and olanzapine**; moderate risk with risperidone, paliperidone, quetiapine; lower risk with aripiprazole, brexpiprazole, cariprazine, lurasidone, ziprasidone, and lumateperone. [1-2]

- **Baseline:** BMI/waist circumference, fasting glucose (or HbA1c), fasting lipid panel, blood pressure. [3]
- **Follow-up:** Weight monthly $\times$ 3 months, then quarterly. Fasting glucose and lipids at 3 months, then annually. [3-4]
- **Management:** Prevention is easier than treatment — switch to a lower-risk agent

early if weight gain $\geq 7\%$ of baseline BMI. If switching is not feasible, **metformin** (1000–2000 mg/day) is the best-studied pharmacologic intervention. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) show comparable or superior benefit and are under active study. Lifestyle counseling should accompany all antipsychotic prescriptions. [1-2][5]

Extrapyramidal Symptoms (EPS)

- **Acute dystonia:** Treat with **IM benztropine 1–2 mg** or **diphenhydramine 50 mg**; onset within minutes. More common with high-potency first-generation agents. [1]
- **Drug-induced parkinsonism (DIP):** Reduce dose or switch antipsychotic; **anticholinergics** (benztropine, trihexyphenidyl) are effective but add anticholinergic burden. [1-2]
- **Akathisia:** Anticholinergics are generally **not** effective. First step is dose reduction or switching. For pharmacologic treatment, **propranolol** (20–80 mg/day), **mirtazapine** (15 mg/day), or **vitamin B₆** (600 mg/day) have the best evidence. Benzodiazepines are second-line. [2][6]
- **Tardive dyskinesia (TD):** Does **not** improve with dose reduction (often worsens). Treat with **VMAT-2 inhibitors** — **valbenazine (Ingrezza)** or **deutetrabenazine (Austedo)**, both FDA-approved. [2][7]

Prolactin Elevation

Highest with risperidone, paliperidone, and asenapine. Can cause galactorrhea, amenorrhea, gynecomastia, sexual dysfunction, and long-term osteoporosis risk. Check prolactin if symptomatic. Management: switch to a prolactin-sparing agent (aripiprazole, quetiapine, clozapine) or add low-dose aripiprazole as a partial D₂ agonist. [1]

QTc Prolongation

Most concerning with **ziprasidone** and **IV haloperidol**. Obtain baseline ECG in patients >40 years or with cardiac risk factors. Avoid combining with other QTc-prolonging agents. [8-9]

Clozapine-Specific Monitoring

- **Agranulocytosis** (~1–2%): ANC monitoring per REMS — **weekly × 6 months → biweekly × 6 months → monthly thereafter**. Clozapine initiation requires baseline ANC $\geq 1500/\mu\text{L}$ ($\geq 1000/\mu\text{L}$ for benign ethnic neutropenia). [10-11]
- **Myocarditis** (~1–3%, highest in first month): Obtain **troponin and CRP at baseline, then weekly × 4 weeks**. Discontinue and obtain cardiology consult if suspected; rechallenge is generally inadvisable. [10][12-13]
- **Seizures:** Dose-related, especially at levels >600 $\mu\text{g/L}$. Consider prophylactic valproate if dose >600 mg/day. [13]
- **GI hypomotility/ileus:** Potentially fatal. Proactive bowel regimen (docusate +

senna) recommended, especially with concurrent anticholinergics. [10][13]

- **Metabolic effects:** Worst in class for weight gain and diabetes risk.

MAJOR DEPRESSIVE DISORDER (MDD)

- **SSRIs and SNRIs** remain first-line. No single agent is clearly superior; choose based on side-effect profile, cost, drug interactions, and prior response. [7]
- When an SSRI fails, **dose optimization alone is generally insufficient** — switching (e.g., to venlafaxine) or augmentation is more effective. [8]
- For **augmentation of treatment-resistant depression**, atypical antipsychotics have the strongest evidence: **aripiprazole** (NNT ~8 for response), **quetiapine** (NNT ~9), **cariprazine**, and **brexpiprazole** are all FDA-approved adjuncts. Weigh metabolic side effects. [9-10]
- **Bupropion augmentation** is a reasonable antidepressant-class augmentation strategy with fewer sexual side effects and weight gain; it was comparable to aripiprazole augmentation in older adults. [9][11]
- **Lithium augmentation** remains a guideline-supported option, particularly in patients with suicidality, though it is underutilized. [12]
- **Esketamine (Spravato)** is FDA-approved for treatment-resistant depression and MDD with acute suicidal ideation; it requires REMS-certified clinic administration. [10]
- Allow **4–6 weeks at an adequate dose** before declaring a trial a failure; ~one-third of patients will need a second-step strategy. [11]

GENERALIZED ANXIETY DISORDER (GAD)

- **SSRIs and SNRIs** are first-line. FDA-approved options include **escitalopram**, **paroxetine**, **duloxetine**, and **venlafaxine**; sertraline and fluoxetine are also effective off-label. [13-14]
- **Start at half the usual dose** — patients with anxiety are more sensitive to activating side effects (jitteriness, palpitations), which mimic anxiety and drive premature discontinuation. [15-16]
- Anxiolytic effects take **2–4 weeks to begin** and up to **3 months for full effect**; titrate to at least a moderate dose before deeming a trial ineffective. [13]
- **Benzodiazepines are not more effective than antidepressants** for GAD and should not be first-line due to dependence, withdrawal, and rebound anxiety. They

do not shorten the duration of SSRI treatment when co-prescribed. [17]

- **Buspirone** is an option but has mixed evidence; it may be most useful as an adjunct or in patients who cannot tolerate SSRIs/SNRIs. [14]
- **Pregabalin** has demonstrated efficacy in meta-analyses but is second-line due to sedation, weight gain, and abuse potential. [17-18]
- Bupropion and vortioxetine have **not** consistently shown efficacy for GAD and are not recommended. [14]
- Continue treatment for **at least 6–12 months** to minimize relapse; experts recommend longer remission periods before tapering compared with depression. [15][17]

Hyponatremia (SIADH)

All SSRIs and SNRIs carry risk; **duloxetine, escitalopram, and venlafaxine** may carry the highest risk, while **bupropion and paroxetine** appear to carry the lowest. [14-15] Risk is greatest in patients **≥60 years**, those on thiazide diuretics, and in the first 30 days. [14][16]

- **Check sodium** at baseline in elderly patients and within 2–4 weeks of initiation. Recheck if symptoms develop (confusion, falls, nausea, headache). [15-16]

Sexual Dysfunction

Affects 30–70% of patients on SSRIs/SNRIs. Management options: dose reduction, switch to **bupropion** (lowest sexual side effects), **mirtazapine**, or **vilazodone/vortioxetine** (lower rates). Augmentation with bupropion may help. [9]

QTc Prolongation

Citalopram has the strongest signal — FDA-mandated max dose of **40 mg/day** (20 mg in patients >60 years, hepatic impairment, or CYP2C19 poor metabolizers). Trazodone also carries QTc risk. Obtain ECG if combining with other QTc-prolonging agents. [9][17]

Serotonin Syndrome

Risk increases with combinations of serotonergic agents (SSRIs + tramadol, triptans, MAOIs, linezolid, lithium). Classic triad: **mental status changes, autonomic instability, neuromuscular hyperactivity** (clonus, hyperreflexia). Treatment: discontinue offending agents, supportive care, **cyproheptadine** for moderate-severe cases. [18]

Discontinuation Syndrome

Most common with **paroxetine and venlafaxine** (short half-lives). Symptoms: dizziness, nausea, "brain zaps," irritability. Taper over **≥2–4 weeks**; fluoxetine (long half-life) rarely causes this.

Blood Pressure — SNRIs

Venlafaxine, duloxetine, desvenlafaxine, and levomilnacipran can cause **dose-dependent hypertension** (especially venlafaxine >300 mg/day). Monitor BP at baseline and after dose changes. [9][17]

Bupropion

Dose-dependent **seizure risk** — contraindicated in patients with seizure disorders, eating disorders (bulimia/anorexia), or abrupt alcohol/benzodiazepine withdrawal. Max single dose 150 mg IR / 450 mg total daily. [9]

BIPOLAR DISORDER

- **Lithium, valproate, and quetiapine** have the broadest evidence for preventing both manic and depressive episodes and are preferred monotherapies for maintenance. [19-20]
- **Lamotrigine** prevents depressive but not manic episodes — ideal for bipolar II or depression-predominant bipolar I. It requires slow titration (risk of Stevens-Johnson syndrome). [19]
- For **acute mania**: lithium, valproate, and atypical antipsychotics (aripiprazole, risperidone, quetiapine, asenapine, cariprazine) are first-line, alone or in combination. [21]
- For **acute bipolar depression**, five agents are FDA-approved: **quetiapine, lurasidone, cariprazine, lumateperone, and olanzapine-fluoxetine combination**. Lurasidone and cariprazine are generally preferred due to lower metabolic burden. [21]
- **Antidepressant monotherapy is contraindicated** in bipolar I (risk of mania switch); antidepressants may be cautiously combined with a mood stabilizer in bipolar II. [21]
- **Discontinue stimulants and antidepressants** during manic/hypomanic episodes. [21]
- **Quetiapine + lithium/valproate** had the strongest evidence for combination maintenance therapy, preventing both mania (HR 0.27) and depression (HR 0.29). [19]
- Lithium has unique **anti-suicidal properties** — an important consideration in high-risk patients. [21]

LITHIUM (Bipolar)

Lab Monitoring Schedule

- **Baseline**: BMP (creatinine, eGFR, calcium), TSH, CBC, pregnancy test,

urinalysis. [4][8][18]

- **Serum lithium levels:** 5 days after dose change, then **every 3 months** once stable (12-hour trough). [19-20]
- **Renal function (creatinine/eGFR):** Every **6 months**. [20-21]
- **TSH:** Every **6 months** (hypothyroidism in ~25% with lab abnormalities, ~4% clinical). [20][22]
- **Calcium:** Every **6–12 months** (hyperparathyroidism with long-term use). [18][21]

Key Adverse Effects and Management

- **Toxicity** (levels ≥ 1.5 mEq/L): Coarse tremor, vomiting, diarrhea, confusion, ataxia → seizures, coma. Precipitated by dehydration, NSAIDs, ACE inhibitors, thiazides, low-salt diets. Educate patients to maintain hydration and salt intake. [18][23]
- **Hypothyroidism:** Treat with levothyroxine; lithium need not be discontinued. Target TSH ~ 1.0 mEq/L if replacing. [22][24]
- **Nephrogenic diabetes insipidus** (polyuria/polydipsia): Mostly reversible. Use once-daily dosing and lowest effective dose. **Amiloride** is the treatment of choice if persistent. [18][22]
- **Chronic kidney disease:** Risk increases after 6–10 years; eGFR declines $\sim 0.9\%$ /treatment year. Preventive strategy: target lower serum levels (0.4–0.6 mEq/L) when possible. Avoid nephrotoxic co-medications. [22][24]
- **Teratogenicity:** Ebstein's anomaly risk $\sim 1:1000$ (lower than previously thought). Discuss with women of childbearing age; not an absolute contraindication in pregnancy. [23]
- **Fine tremor:** Common, dose-related. Reduce dose or add low-dose propranolol. [23]

VALPROATE (Bipolar)

Lab Monitoring

- **Baseline:** CBC with differential, LFTs, pregnancy test (mandatory in women of childbearing potential), coagulation studies. [4][8][25]
- **Serum valproate levels:** Target **50–100 $\mu\text{g/mL}$** (acute mania); obtain 3–5 days after dose change, then every **3–6 months**. [19]
- **LFTs and CBC:** Every **3–6 months**. [4]
- **Ammonia level:** Check if unexplained lethargy, vomiting, or mental status changes (hyperammonemic encephalopathy can occur even with normal LFTs, especially

with concurrent topiramate). [25-26]

Key Adverse Effects

- **Teratogenicity: 8.6% malformation rate** (neural tube defects, cardiac anomalies, reduced IQ, neurodevelopmental disorders). **Should not be prescribed to women of childbearing potential** unless no alternative exists and effective contraception is co-prescribed. [27-29]
- **Hepatotoxicity:** Rare but potentially fatal (1:20,000 general population; 1:500 in high-risk groups — children <2 years on polytherapy). Monitor LFTs; discontinue if transaminases rise >3× ULN with symptoms. [25][27]
- **Pancreatitis:** Rare (1:40,000). Warn patients about abdominal pain, nausea, vomiting. [25][27]
- **Thrombocytopenia and coagulopathy:** Monitor platelet count and coagulation studies, especially preoperatively. [25]
- **Polycystic ovary syndrome (PCOS):** Increased risk in young women — menstrual irregularities, hyperandrogenism, weight gain. Consider alternative mood stabilizers in this population. [28-29]
- **Weight gain and tremor:** Common; dose-related.

ADHD

- **Stimulants (methylphenidate and amphetamines)** are first-line with the largest effect sizes and consistent evidence for improved executive functioning. [22-23]
- Long-acting formulations are generally preferred for adherence, smoother symptom control, and lower abuse potential. Lisdexamfetamine is a prodrug with inherently lower abuse liability.
- **Nonstimulant options** when stimulants are contraindicated, not tolerated, or ineffective: **atomoxetine** (FDA-approved; takes 1–2 weeks for full effect), **viloxazine (Qelbree)** (FDA-approved for adults and children ≥6), and **bupropion** (off-label). [10][22][24]
- **Alpha-2 agonists (guanfacine, clonidine)** are useful adjuncts to stimulants, especially with comorbid aggression, insomnia, or tics; less evidence in adults as monotherapy. [23]
- In patients with **comorbid substance use disorder**, nonstimulants (atomoxetine) or extended-release formulations with lower abuse potential are preferred. [25]
- In patients with **comorbid anxiety/depression**, atomoxetine, viloxazine, or bupropion may address both conditions. [22]

- Monitor blood pressure and heart rate; large-scale registry studies have been reassuring regarding serious cardiovascular events with stimulants. [23]
- Use **controlled substance agreements and prescription drug monitoring programs** to mitigate misuse/diversion risk. [22]

STIMULANTS (ADHD)

Monitoring

- **Baseline:** Heart rate, blood pressure, height, weight, cardiac history (personal and family — sudden death, WPW, HCM, long QT). **No routine ECG or blood tests** required unless clinically indicated. [30-31]
- **Follow-up:** HR and BP at each dose change and every **6 months**. Height every 6 months in children; weight every 3 months (children ≤ 10) or every 6 months (older children/adults). [31-32]

Key Adverse Effects and Management

- **Appetite suppression/weight loss:** Take medication with or after meals; add calorie-dense snacks in the evening when medication wears off; consider drug holidays during school breaks if growth is a concern. [31]
- **Growth suppression:** ~1–2 cm reduction in predicted adult height with consistent long-term use; effect attenuates after ~3 years. Consider drug holidays if height falls below expected percentiles. [30-31][33]
- **Insomnia:** Use long-acting morning formulations; avoid afternoon dosing of short-acting agents. **Melatonin** is a reasonable adjunct. If persistent, consider switching to atomoxetine or guanfacine. [31]
- **Cardiovascular:** Average increases of 1–2 bpm HR and 1–4 mmHg BP; 5–15% of patients have more substantial increases. If sustained resting tachycardia >120 bpm or systolic BP >95 th percentile on two occasions, reduce dose and refer. [30-31]
- **Tics:** Stimulants do not cause tics but may unmask them. Monitor for 3 months before changing treatment. If stimulant-related, switch to guanfacine, atomoxetine, or clonidine. [31]
- **Psychotic symptoms:** Rare ($<1\%$); discontinue stimulant, symptoms typically resolve. May rechallenge cautiously once resolved. [31][34]

AUTISM SPECTRUM DISORDER (ASD)

- **No medications treat core ASD deficits** (social communication, restricted interests). Pharmacotherapy targets comorbid symptoms. [26]
- For **irritability and aggression:** **risperidone and aripiprazole** are the only FDA-

approved medications, with large effect sizes (~1.1–1.2) but significant metabolic side effects (weight gain, hyperglycemia, dyslipidemia). [27]

- For **comorbid ADHD symptoms in ASD**: methylphenidate and atomoxetine are effective, though response rates are lower and adverse event rates higher than in neurotypical ADHD. Stimulants may cause more **behavioral activation** (restlessness, disinhibition) in ASD. [26-28]
- Expert consensus recommends **stimulant trial first**, then alpha-2 agonist or atomoxetine if stimulants fail. Atomoxetine may also reduce stereotyped behaviors and social withdrawal. [26][29]
- **Guanfacine extended-release** showed a large effect size (1.2) for ADHD symptoms in ASD in one RCT. [27]
- **Melatonin** is useful for the sleep disturbances common in ASD. [27]

SUBSTANCE USE DISORDERS

Alcohol Use Disorder (AUD):

- **Oral naltrexone 50 mg/day** is first-line — once-daily dosing, NNT of 11 to prevent return to heavy drinking. Contraindicated with opioid use or acute hepatitis/liver failure. [30-31]
- **Acamprosate** (666 mg TID) is an effective alternative, especially when naltrexone is contraindicated (e.g., liver disease); NNT of 11 for preventing return to any drinking. The TID dosing and diarrhea are barriers. [31]
- **Topiramate** has moderate evidence as a second-line agent for reducing drinking days and heavy drinking days. [30][32]
- **Gabapentin** is endorsed as an option when first-line agents are contraindicated or ineffective, particularly in patients with prominent withdrawal symptoms. [32-33]
- **Disulfiram** is most effective in supervised settings; evidence for unsupervised use is limited. [33]

Opioid Use Disorder (OUD):

- **Buprenorphine and methadone** are first-line, reducing all-cause mortality by ~60% and ~50%, respectively. The X-waiver has been eliminated — any DEA-licensed prescriber can prescribe buprenorphine. [34-35]
- **Methadone** requires dispensing through licensed opioid treatment programs; higher doses (60–100 mg/day) are associated with better outcomes. [36]
- **Extended-release injectable naltrexone** is a third-line option; oral naltrexone is no more effective than placebo for OUD. Requires 7–10 days opioid-free before

- initiation to avoid precipitated withdrawal. [34][37]
- **Low-dose buprenorphine initiation ("microdosing")** is an emerging strategy to avoid precipitated withdrawal, particularly important in the fentanyl era. [38]
- Naloxone distribution should be offered to all patients with OUD. [35]

Stimulant Use Disorder:

- **No FDA-approved medications** exist. Combination **bupropion + injectable naltrexone** and **mirtazapine** show promise. [35]

SUBSTANCE USE DISORDER MEDICATIONS

Naltrexone (AUD and OUD)

- **Labs:** LFTs at baseline; periodic monitoring recommended. Contraindicated in **acute hepatitis or severe hepatic impairment**. [35-36]
- Must be **opioid-free for 7–14 days** before initiation to avoid precipitated withdrawal. Consider a 25 mg test dose or urine drug screen before full dosing. [36-37]
- Key adverse effects: nausea, headache, dizziness. Warn patients that **opioid tolerance is lost** — risk of fatal overdose if opioids are resumed after discontinuation. [37]

Acamprosate (AUD)

- **Contraindicated in severe renal insufficiency** ($\text{CrCl} \leq 30 \text{ mL/min}$); dose-adjust for moderate impairment. No hepatic concerns — preferred over naltrexone in liver disease. [36-37]
- Main adverse effect: **diarrhea** (dose-limiting in some patients). [37]

Buprenorphine (OUD)

- **Labs:** LFTs at baseline; monitor periodically. CYP450 interactions possible. [38]
- Key adverse effects: headache, nausea, constipation, sweating, endocrine suppression (decreased libido, amenorrhea), sublingual dental erosion/caries (FDA warning for sublingual formulations). [38]
- **Precipitated withdrawal** risk if initiated while full agonist opioids are still on board — particularly problematic with fentanyl (long tissue half-life). Low-dose initiation ("microdosing") strategies can mitigate this. [38]

Methadone (OUD)

- **Labs:** Baseline ECG recommended (QTc prolongation risk); repeat ECG at 30 days

and annually, or with dose changes >40 mg. LFTs at baseline. [38]

- **QTc prolongation and torsades de pointes:** Avoid if QTc >500 ms. Caution with concurrent QTc-prolonging medications (antipsychotics, certain antidepressants). [38]
- **Respiratory depression:** Risk highest during initiation and dose increases, especially with concurrent benzodiazepines or alcohol. [38]
- Endocrine suppression similar to buprenorphine.

Table 3. Management of Adverse Events during Treatment with ADHD Medications.*	
Adverse Event	Suggested Management Strategy
Decreased appetite, deficits in height and weight gain	Measure height every 6 mo in children and young people. Measure weight every 3 mo in children ≤10 yr old; at 3 mo and 6 mo after starting treatment in children >10 yr old and young people, and every 6 mo thereafter (or more often if concerns arise); and every 6 mo in adults. If weight loss is of clinical concern, recommend that medication be taken either during or after meals rather than before meals; suggest additional meals or snacks early in the morning or late in the evening, when stimulant effects have worn off; obtain dietary advice from a dietician; recommend high-calorie foods of good nutritional value; suggest a planned break from treatment; or change medication. If a child's height is lower than expected for age, consider a planned break in treatment during school holidays. Refer to pediatric endocrinologist or growth specialist if height and weight values are below critical thresholds (Section S6).† If weight changes in an adult as a result of ADHD pharmacologic treatment, change medication.
Increased blood pressure or heart rate	Do not obtain routine blood tests or electrocardiogram unless there is a clinical indication. Measure heart rate and blood pressure after each dose change and every 6 mo. If sustained resting tachycardia (>120 beats/min), arrhythmia, or systolic pressure >95th percentile (or a clinically significant increase) on two occasions, reduce dose and refer patient to a specialist (Fig. S1). If sustained orthostatic hypotension or fainting with guanfacine, reduce dose or switch to another ADHD medication.
Sleep disturbance	If behavioral measures (sleep hygiene) are insufficient and it is not convenient to stop medication, review the possible causes of sleep problems: treat restless legs syndrome if present; if stimulants cause a rebound effect, add small doses of short-acting stimulants in the evening; if the current treatment is a stimulant, consider a reduced dose, alternative stimulant class or formulation, or atomoxetine; consider adding melatonin.†
Tics	Monitor tics over a 3-mo period before making any decision regarding ADHD treatment.† If tics are stimulant-related, reduce the stimulant dose or consider changing to guanfacine (in children ≥5 yr of age and young people only), atomoxetine, or clonidine; adding an antipsychotic agent†; or stopping medication.
Seizures	If seizures are new or worsening, review ADHD medication and stop any medication that might be contributing to the seizures; cautiously reintroduce ADHD medication if it is unlikely to be the cause of the seizures.
Psychotic symptoms	If symptoms occur with a therapeutic dose of ADHD medication, reduce the dose† or discontinue the drug (Section S6). Once psychotic symptoms resolve, consider rechallenge with ADHD medication.

* Except as otherwise noted, recommendations are from the National Institute for Health and Care Excellence (NICE) guidelines.⁴

† The recommendation is from the European ADHD Guidelines Group.¹⁷

Table 3. Management of Adverse Events during Treatment with ADHD Medications.*

[Pharmacologic Treatment of Attention Deficit–Hyperactivity Disorder](#). N Engl J Med. September 9, 2020.

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CYP450 INTERACTIONS — THE MASTER TABLE

The CYP450 system mediates the majority of clinically significant pharmacokinetic interactions in psychopharmacology. The following table summarizes the most important inhibitors and inducers encountered in psychiatric practice

CYP Enzyme	Strong Inhibitors (↑ substrate levels)	Strong Inducers (↓ substrate levels)	Key Psychotropic Substrates	References
1A2	Fluvoxamine, ciprofloxacin	Smoking (tobacco), omeprazole	Clozapine, olanzapine, duloxetine, mirtazapine	[1-3]
2D6	Fluoxetine, paroxetine, bupropion, duloxetine	None clinically significant	Aripiprazole, risperidone, iloperidone, haloperidol, venlafaxine, atomoxetine, TCAs	[4-6]
3A4	Fluvoxamine, nefazodone, ketoconazole, grapefruit juice	Carbamazepine, phenytoin, phenobarbital, St. John's Wort	Quetiapine, lurasidone, ziprasidone, buspirone, alprazolam, midazolam, sertraline	[7-9]
2C19	Fluvoxamine, fluoxetine	Carbamazepine	Citalopram, escitalopram, sertraline, diazepam, vortioxetine	[4-5]

QUICK-REFERENCE: TOP 10 "NEVER MISS" INTERACTIONS

1. **Fluvoxamine + clozapine** → clozapine toxicity (CYP1A2 inhibition) [10]
2. **Smoking cessation + clozapine/olanzapine** → toxicity (CYP1A2 de-induction) [4][6]
3. **Carbamazepine + nearly everything** → subtherapeutic levels of co-prescribed drugs [7-8]
4. **Valproate + lamotrigine** → doubled lamotrigine levels → SJS/TEN risk [19]
5. **Fluoxetine/paroxetine + aripiprazole/risperidone** → elevated antipsychotic levels (CYP2D6) [3]
6. **Lithium + NSAIDs/thiazides/ACEi** → lithium toxicity [14]
7. **Lithium + SSRIs** → serotonin syndrome risk [14-15]
8. **Benzodiazepines + methadone/buprenorphine** → respiratory depression/death [29][32]
9. **Methadone + CYP3A4 inducers** → opioid withdrawal; stopping inducer → overdose [29-30]
10. **Oral contraceptives + carbamazepine or lamotrigine** → contraceptive failure / mood destabilization [19][22-23]

ANTIPSYCHOTIC + ANTIDEPRESSANT COMBINATIONS

CYP2D6-Mediated Interactions (Most Common)

Fluoxetine and paroxetine are potent CYP2D6 inhibitors and will significantly raise levels of aripiprazole, risperidone, iloperidone, and haloperidol. The aripiprazole FDA label recommends **halving the dose** when co-prescribed with a strong CYP2D6 inhibitor. Risperidone levels can increase 75–100%, increasing EPS and prolactin elevation risk. [3]

- **Safer SSRI choices** when combining with CYP2D6-substrate antipsychotics: **escitalopram, citalopram, or sertraline** (at doses ≤150 mg/day), which have negligible-to-mild CYP2D6 inhibition. [2]

CYP1A2-Mediated Interactions

Fluvoxamine is a potent CYP1A2 inhibitor and can cause **3- to 10-fold increases** in clozapine levels — this combination should generally be avoided or requires aggressive level monitoring and dose reduction. [10] Fluvoxamine also markedly raises olanzapine levels.

CYP3A4-Mediated Interactions

Lurasidone and quetiapine are primarily CYP3A4 substrates. **Lurasidone is**

contraindicated with strong CYP3A4 inhibitors (ketoconazole, clarithromycin) and strong inducers (carbamazepine, rifampin). Quetiapine levels can increase 6-fold with ketoconazole. [11]

Pharmacodynamic Interactions

- **QTc prolongation:** Additive risk when combining antipsychotics with SSRIs, particularly citalopram. A 2026 cohort study found that concomitant antipsychotic + SSRI use was associated with increased ventricular arrhythmia and sudden death risk compared with antipsychotic use alone, with the highest risk in the first 30 days of co-prescription. [12]
- **Serotonin syndrome:** Low but real risk when combining antipsychotics that have serotonergic activity (e.g., ziprasidone, lurasidone) with SSRIs/SNRIs. [13]
- **Additive sedation:** Mirtazapine + quetiapine was the most common drug pair associated with tachycardia and QT prolongation in a European pharmacovigilance analysis. [13]

MOOD STABILIZER INTERACTIONS

Lithium

Lithium has a narrow therapeutic index and is **renally cleared** — it has few CYP450 interactions but critical pharmacokinetic and pharmacodynamic ones. [14]

- **Drugs that raise lithium levels** (risk of toxicity): NSAIDs, thiazide diuretics, ACE inhibitors/ARBs, metronidazole. Obtain lithium level within 5 days of adding any of these. [14]
- **Lithium + SSRIs/SNRIs:** Increased risk of **serotonin syndrome**. The FDA label warns of this with all serotonergic agents. Monitor for tremor, myoclonus, hyperreflexia, agitation. The combination is commonly used and generally safe with monitoring, but clinicians should educate patients on warning signs. [14-16]
- **Lithium + antipsychotics:** Reports of an **encephalopathic syndrome** (weakness, lethargy, fever, confusion, EPS) — historically described with haloperidol but reported with other antipsychotics. Monitor closely for neurological toxicity, especially at higher lithium levels. [14][17]
- **Lithium + carbamazepine:** Increased risk of **neurotoxic side effects** (ataxia, tremor, nystagmus, confusion) even at therapeutic levels of both drugs. [7][18]

Valproate

- **Valproate + lamotrigine:** Valproate **doubles lamotrigine levels** by inhibiting glucuronidation. This dramatically increases the risk of **Stevens-Johnson syndrome/toxic epidermal necrolysis**. When co-prescribed, the lamotrigine

starting dose and titration must be halved (start at 25 mg every other day). [19-20]

- **Valproate + carbamazepine:** Carbamazepine induces valproate metabolism (lowering levels) while valproate inhibits epoxide hydrolase, raising levels of the toxic metabolite **carbamazepine-10,11-epoxide** — can cause toxicity (diplopia, ataxia, nausea) even with "normal" carbamazepine levels. [9]
- **Valproate + lithium:** Case reports of valproate-induced **hyperammonemic encephalopathy** precipitated by lithium initiation, possibly via lithium-mediated increases in valproate levels. Check ammonia if confusion develops. [21]

Carbamazepine — The "Universal Inducer"

Carbamazepine is a potent inducer of CYP3A4, CYP2C9, CYP1A2, and UGT enzymes.

It **lowers levels of nearly every co-prescribed psychotropic**, including: [7-9]

- Antipsychotics: clozapine, olanzapine, haloperidol, risperidone, paliperidone, quetiapine, ziprasidone, aripiprazole
- Antidepressants: bupropion, citalopram, sertraline, trazodone, mirtazapine, TCAs
- Other mood stabilizers: lamotrigine (↓40%), valproate
- Benzodiazepines: alprazolam, clonazepam, midazolam
- **Oral contraceptives** — renders hormonal contraception unreliable [22-23]
- **Buprenorphine and methadone** — can precipitate opioid withdrawal [7]

Pearl: When carbamazepine is **discontinued**, levels of all co-prescribed medications will **rise** over 1–2 weeks — monitor for toxicity.

Lamotrigine

- Lamotrigine is metabolized by glucuronidation (UGT), not CYP450, so it has **few outgoing interactions** but is highly susceptible to incoming ones. [19-20]
- **Estrogen-containing oral contraceptives** decrease lamotrigine levels by ~50% (via UGT induction). Conversely, during the pill-free week, lamotrigine levels rise — creating cyclical mood instability. Dose adjustments or non-hormonal contraception are recommended. [19][23]

SMOKING (TOBACCO) AND CYP1A2

This is one of the most underappreciated interactions in psychiatry. **Polycyclic aromatic hydrocarbons** in tobacco smoke (not nicotine itself) induce CYP1A2. As few as **7–12 cigarettes/day** produce maximal induction. [4-5][24]

- **Clozapine:** Smokers require roughly **double the dose** of non-smokers. Smoking

cessation can cause clozapine levels to rise by **50–72%** within days, risking seizures, sedation, and toxicity. Reduce clozapine dose by ~30–50% upon smoking cessation and monitor levels closely. [4][6][25]

- **Olanzapine:** Similar effect — reduce dose by ~30% in non-smokers vs. smokers. [5-6]
- **Nicotine replacement therapy (patches, gum) does NOT induce CYP1A2** — it is the combustion products, not nicotine. Switching from cigarettes to NRT or e-cigarettes (without combustion) has the same effect as smoking cessation and requires dose reduction. [4-5]
- **Inflammation** (e.g., infections, COVID) **suppresses** CYP1A2, further raising clozapine levels — a "double hit" if a smoking patient develops pneumonia and stops smoking simultaneously. [26]

STIMULANTS (ADHD) — INTERACTIONS

Stimulants have relatively **few CYP450 interactions** compared with other psychotropic classes, but important pharmacodynamic interactions exist.

- **Stimulants + MAOIs: Absolutely contraindicated** — risk of hypertensive crisis. Allow ≥14 days washout.
- **Stimulants + mood stabilizers:** Mixed amphetamine salts can be safely combined with valproate without precipitating mania, based on limited controlled data. No significant pharmacokinetic interaction between stimulants and lithium or valproate. [27-28]
- **Atomoxetine** is a CYP2D6 substrate — levels increase 6- to 8-fold with strong CYP2D6 inhibitors (fluoxetine, paroxetine). Reduce atomoxetine dose by ~50% when co-prescribed. [2]
- **Stimulants + antipsychotics:** Pharmacodynamic opposition (dopamine agonism vs. antagonism). In practice, this combination is used in patients with comorbid ADHD and psychotic disorders, but efficacy of both agents may be blunted.

SUBSTANCE USE DISORDER MEDICATIONS — INTERACTIONS

Methadone

Methadone is metabolized by CYP3A4, CYP2B6, CYP2C19, and CYP2D6 — making it vulnerable to numerous interactions. [29]

- **CYP3A4 inducers** (carbamazepine, phenytoin, rifampin, St. John's Wort) can precipitate **opioid withdrawal** by lowering methadone levels. Conversely, stopping

an inducer without reducing methadone can cause **overdose**. [7][29-30]

- **Benzodiazepines + methadone:** Strongly associated with overdose death. Avoid when possible; if co-prescribed, use lowest effective benzodiazepine dose with close monitoring. [29]
- **QTc-prolonging drugs** (antipsychotics, citalopram, TCAs) + methadone: Additive QTc risk. Obtain ECG before and after adding QTc-prolonging co-medications. [29]
- **Quetiapine + methadone:** Identified as a signal for increased overdose risk in pharmacoepidemiologic screening — likely via additive sedation and possible CYP3A4 competition. [31]

Buprenorphine

- **Benzodiazepines and other CNS depressants** (including gabapentinoids, antipsychotics, alcohol): Increased risk of respiratory depression, sedation, and death. However, the FDA label explicitly states that buprenorphine treatment **should not be categorically denied** to patients taking these medications — the risk of untreated OUD is greater. Use clinical judgment, monitor closely, and taper CNS depressants when feasible. [32-33]
- **CYP3A4 inhibitors** (ketoconazole, some protease inhibitors) can raise buprenorphine levels; **CYP3A4 inducers** (carbamazepine, phenytoin) can lower them and precipitate withdrawal. [7][32]
- **Clonidine + buprenorphine:** Pharmacoepidemiologic signal for increased opioid overdose risk — likely additive sedation and hypotension. [31]

Naltrexone

- **Opioid-containing medications** (codeine, tramadol, opioid-containing cough suppressants): Naltrexone blocks opioid receptors and renders these medications **ineffective for analgesia**. Ensure patients and all treating providers are aware.

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