SSRIs and SNRIs: What You Should Know About the Risks

A Guide for Patients and Families

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December 2025

SSRIs and SNRIs are among the most heavily prescribed drugs for depression and anxiety, but large meta-analyses show they help only about **15% more people than placebo**, while exposing all users to substantial risks[1,2]. This handout summarizes those risks so you can decide whether starting or staying on these medications is worth it for you.

How These Drugs Change the Brain

SSRIs and SNRIs chronically raise serotonin (and, for SNRIs, norepinephrine), so the brain **always** adapts to their presence. In a significant subset of people, these adaptations become *oppositional* (the brain actively pushes back against the drug's effects)—altering dopamine, glutamate, GABA, histamine, acetylcholine, and stress-hormone systems in ways that can blunt emotions, sap energy, destabilize mood, and make stopping the medication difficult[3–7].

Major Long-Term Harms

- **Sexual dysfunction (sometimes permanent)**
  Careful studies find 40–80% of people on these drugs develop reduced desire, genital numbness, delayed or absent orgasm, or erectile problems[8–10]. A recognized condition—post-SSRI sexual dysfunction (PSSD)—means sexual problems can persist for months or years after stopping, and regulators now warn that antidepressant-related sexual effects may be long-lasting[11–14].
- **Weight gain, insulin resistance, and diabetes**
  Large cohorts show slow, ongoing weight gain, especially with paroxetine and escitalopram, and an increased risk of gaining ≥5% of body weight within 6–12 months[15–18]. Laboratory work shows SSRIs can directly impair insulin secretion and β-cell insulin action in vitro[19], and observational data link long-term antidepressant use to higher rates of type 2 diabetes, suggesting the diabetes risk is not just from weight gain[20].
- **Sleep disruption, fatigue, and low drive**
  Sleep studies show less REM sleep, less deep slow-wave sleep, more awakenings, and overall lighter, non-restorative sleep[21–23]. Many people describe "tired but wired" nights and daytime exhaustion, reflecting both broken sleep architecture and dampening of dopamine and norepinephrine—the brain chemicals that normally drive alertness, energy, and motivation[24].
- **Emotional numbing and cognitive problems**
  Surveys find 40–70% of people taking antidepressants feel emotionally "numb," "flat," or "not like myself," and up to half cite blunted emotions as a reason for stopping[25–28]. A sizeable subgroup develops memory problems, slowed thinking, learning difficulties, and "brain fog," especially at higher doses or with long-term use[29–33].
- **Movement disorders and akathisia**
  These drugs can cause akathisia—intense inner restlessness and agitation—that is closely linked to emergent self-harm and suicidality[34–3734–37]. Dystonias and myoclonus also occur and may be misread as primary neurological disease.
- **Systemic medical risks**
  Long-term use is associated with 30–70% higher fracture risk, increased bleeding, QTc prolongation (notably with citalopram/escitalopram), hyponatremia, rashes, possible cataracts, and neonatal complications when used in pregnancy[38–47]. New medical symptoms that start on these drugs should always be suspected as drug effects.

Mood Cycling, Glutamate, and Suicidality

Many people told they have "recurrent depression" actually have underlying mood cyclicity—often driven by glutamate, a brain chemical that builds new neural pathways. When glutamate is overactive, it can rapidly wire in patterns that support mood cycling, bypassing the stable networks that normally anchor circadian rhythm and steady mood—even if the person has **never** had obvious hypomanic or manic symptoms[48–50]. In these patients, antidepressants can:

- Make mood less stable
- Trigger mixed states (agitated depression)[51–53]
- Increase irritability layered onto depression, consistent with work reconceptualizing "agitated unipolar depression" as a depressive mixed state[54,55]
- **Increase the frequency of depressive recurrences over time**, even in people with no prior hypo/mania, likely driven by upregulated glutamate signaling and new neural networks that support cyclicity[3–7,51,52,56–59].

In children, adolescents, and young adults, these drugs raise the risk of suicidal thoughts and behaviors, and risk is highest when they are used alone (without a mood stabilizer) in people with cycling mood patterns.[57,58,60]. When suicidality emerges

on treatment, it often follows an "activation" picture—akathisia, agitation, and impulsive urges shortly after starting or increasing the dose.

Withdrawal, Recurrence, and PAWS

Because the brain adapts to chronic exposure, stopping SSRIs and SNRIs is often **much harder** than starting them.

- **Acute withdrawal:** Dizziness, "brain zaps," insomnia, panic-level anxiety, flu-like symptoms, and sensory changes typically start within days of dose reduction and can last weeks[3,61–63]. Around 40–50% of patients develop a withdrawal syndrome, with real-world surveys and systematic reviews reporting even higher and often severe rates[61,62,64–66]. Recent reviews and cohort work confirm that antidepressant discontinuation syndrome is common, often prolonged, and frequently under-recognized in routine care[63,67].
- **Relapse vs recurrence vs cycling:**
  - *Withdrawal* is tightly tied to dose changes and improves if the taper is slowed or a small dose is reinstated.
  - *Relapse* is the original episode returning within 6–9 months of remission.
  - *Recurrence* is a new episode after a period of stability—and rising recurrence frequency on long-term antidepressants may reflect drug-driven mood cycling, including in glutamate-dominant people with no past hypo/mania.[3–7,56–58,68,69].
- **Post-acute withdrawal syndrome (PAWS):**
  A minority develop long-lasting waves of severe mood, cognitive, autonomic, pain, and sexual symptoms that can persist months to years after stopping, distinct from ordinary depression[6,70,71]. One small cohort reported PAWS in 15% of panic-disorder patients, lasting up to 166 months[71].

If You Are Considering or Already Taking These Drugs

Given that SSRIs and SNRIs help only about **15% more people than placebo** while carrying the above risks, they are a poor first-line choice for most people. Non-drug approaches—psychotherapy, exercise, sleep and circadian repair, trauma-informed work, social and nutritional interventions—deserve full trials before exposing your nervous system to long-term serotonergic manipulation[64,72–74]. In addition, there are other **biological strategies** your clinician can consider, including (Some of these may be unfamiliar; your clinician can explain which might apply to your situation.):

- Glutamatergic approaches (for example, carefully monitored ketamine/esketamine, dextromethorphan, amantadine, minocycline, lamotrigine, or other glutamate-modulating agents)[75–77].
- Dopaminergic and noradrenergic strategies (for example, bupropion, amantadine, levomilnacipran, pramipexole, or psychostimulants in selected cases)[78,79]
- Multimodal monoamine modulators, with downstream effects on multiple neurotransmitter systems, (for example, vortioxetine, viloxazine)[80–85]. Viloxazine is a non-stimulant ADHD medication in the US today, but it was previously sold in Europe for almost three decades as an antidepressant, with trials in adults and older adults showing benefit for endogenous depression and good long-term safety[81,82,86–88]
- Anti-inflammatory and metabolic strategies, (for example, minocycline, omega-3 fatty acids, many other nutraceutical agents, metabolic optimization, and treatment of sleep apnea or insulin resistance)[89–91]

If you are already taking these medications and want to come off, **do not stop suddenly**. Very slow, individualized tapers over many months, with tiny dose reductions, are often needed to reduce withdrawal and PAWS risk; this requires a clinician who understands and respects these dangers[61,66–68].

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