The Art and Science of Deprescribing

At first glance, the term "deprescribing" may seem like a contradiction – after all, prescribing is at the core of psychopharmacology. Yet, stopping a medication is just as much a part of clinical practice as starting one. Whether a medication is being discontinued because it hasn't worked, because it is no longer needed, or simply because the patient has stopped taking it on their own, deprescribing is not an abandonment of treatment but an essential part of psychiatric care.

For decades, the focus in psychiatry has been on initiating treatment – which medication to prescribe, in what dose, and for how long. But what happens when treatment needs to stop? Many clinicians already engage in deprescribing without labeling it as such: switching from one medication to another when the first is ineffective, tapering a medication that has done its job, or managing the aftermath when a patient discontinues on their own. What we have come to recognize is that how a medication is stopped is just as important as how it is started, and that abrupt discontinuation often leads to unnecessary suffering, relapse, and withdrawal syndromes that could have been prevented.

This book serves as a deprescribing guide but is not an argument against medication. Rather, it is a resource for those needing to know when and why to deprescribe each medication. With growing awareness of the risks associated with precipitous discontinuation for some medications (Cosci and Chouinard, 2020; Fava and Cosci, 2019; Rickels et al., 1990), we aim to provide a structured, evidence-based approach to deprescribing – not as an afterthought – but as a deliberate and thoughtful part of psychiatric care.

Finally, deprescribing is not always initiated by the clinician. Patients frequently become "self-deprescribers;" they stop medications due to side effects, lack of efficacy, financial constraints, or simple forgetfulness (Reis et al., 2004, 2010; Zehgeer et al., 2018). When this happens, clinicians are often left managing the fallout rather than guiding the process. A core goal of this book is to provide strategies for both planned discontinuation and damage control when patients stop medications abruptly.

The Decision to Stop Treatment

Discontinuing psychotropic medications represents one of the most important decisions in clinical practice – one that requires a balance between therapeutic benefits and the potential risks of discontinuation. This process is not a simple "on-off" switch; rather, it is a consideration that hinges on multiple clinical, biological, and psychological factors. The clinician's role is not merely to decide when a medication should be stopped but to guide the process in a manner that minimizes relapse, mitigates discontinuation-emergent symptoms, and optimizes long-term treatment outcomes.

When to Consider Stopping Treatment

The decision to discontinue an antidepressant, anxiolytic, or mood stabilizer should begin with an assessment of treatment response. Patients who have achieved full remission and maintained this may be candidates for tapering (Hathaway et al., 2018). However, remission alone is insufficient; stability must be assessed not just in terms of symptom resolution but also through the lens of functional recovery – has the patient returned to baseline occupational, social, and emotional functioning? Have they engaged in psychotherapy and changed behaviors and patterns of thinking or experiencing events? If not, discontinuation may be premature.

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Recent data on anxiety disorders and depression underscore the importance of treatment duration in sustaining remission. For example, in anxiety disorders, extending antidepressant treatment to at least 12 months confers superior long-term outcomes compared to shorter treatment (e.g., 6 months) based on prospective controlled trials (Rickels et al., 2010). The same principle applies to depressive disorders, where extended treatment lowers the risk of recurrence, especially for patients with recurrent depressive episodes, where premature discontinuation can set the stage for a relapsing–remitting course (Gueorguieva et al., 2017).

Moreover, the presence of residual symptoms (e.g., subthreshold depressive or anxious symptoms that persist despite partial response) should signal caution when considering discontinuation. These residual symptoms often serve as precursors to relapse and may indicate the need for ongoing medication rather than premature tapering.

Medication Tolerability and Patient Preferences

Medication tolerability is an important determinant in long-term adherence (Mark et al., 2011; Niarchou et al., 2024). While some patients tolerate psychotropic medications with minimal side effects, others may experience significant burdens, including weight gain, sexual dysfunction, emotional blunting, activation, or cognitive dulling, and this may be particularly problematic in pediatric patients wherein parents are also part of the decision-making process (Baumel et al., 2023; Mills and Strawn, 2019; Strawn et al., 2023). When side effects impair quality of life, the risk–benefit ratio shifts, often making discontinuation a compelling option. Yet, stopping treatment must be weighed against the risk of symptom recurrence.

Patient preference also plays an important role in this equation. Some patients, after experiencing substantial symptom relief, develop a sense of mastery and wish to discontinue medication, believing that they no longer "need" pharmacological intervention. Others may fear the stigma of long-term psychiatric medication use or prefer nonpharmacological strategies such as psychotherapy, lifestyle modifications, or complementary approaches. Engaging in shared decision-making (e.g., educating patients on the risks of relapse, the importance of gradual tapering, and potential withdrawal effects) ensures that discontinuation, if pursued, is both informed and strategic.

When Stopping Isn't the Right Choice: Switching between Medications

In many cases, discontinuation may not be the appropriate course of action, not because the patient requires indefinite pharmacological treatment, but because the current medication is not providing sufficient benefit. Here, the clinical decision shifts from discontinuation to switching strategies.

The prescriber must first determine whether the switch is being driven by a lack of efficacy, side effects, or both. If the current medication is providing partial benefit but is poorly tolerated, a switch within the same pharmacological class (e.g., from one SSRI to another) may be warranted. However, if the medication failed to provide meaningful symptom relief, a shift to a different mechanism of action (e.g., from an SSRI to an SNRI, or from an antidepressant to a second-generation antipsychotic augmentation strategy) may be necessary.

Switching strategies can vary, with three primary approaches, which are discussed within the individual medication monographs that follow:

1. **Cross-titration:** This strategy, often used when switching between medications with overlapping mechanisms (e.g., from one SSRI to another), involves gradually tapering the first medication while simultaneously titrating the second.

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This minimizes withdrawal effects and ensures continuous receptor (target) engagement.

2. **Direct switch:** This method is appropriate when switching between agents with similar pharmacokinetics and receptor profiles (e.g., from lorazepam to clonazepam). A direct switch avoids unnecessary delays but requires close monitoring for emergent side effects or withdrawal symptoms.
3. **Washout period:** Used when switching between medications with significant pharmacological differences (e.g., from an SSRI to a monoamine oxidase inhibitor (MAOI)), this approach involves discontinuing the first medication and waiting for a specified period before starting the next to avoid potentially dangerous drug interactions (e.g., serotonin syndrome).

The choice among these strategies depends on multiple factors, including the pharmacokinetics and pharmacogenetics (in some cases) of the medications involved, the urgency of symptom control, and the patient's prior experiences with medication changes. A well-planned switch, guided by both scientific rationale and clinical judgment, can improve treatment outcomes while minimizing the risks associated with abrupt discontinuation.

Psychological Factors Influencing the Decision to Discontinue Medication

Beyond clinical stability and tolerability, the psychological landscape of discontinuation is complex. A patient's decision to stop medication is not often purely based on symptom status alone; it is intertwined with cognitive biases (Leydon et al., 2007), emotional responses, and interpersonal dynamics (e.g., family reactions and parental perceptions in the case of children and adolescents):

- **Cognitive biases and misattribution:** Patients may misattribute symptom resolution to personal resilience rather than pharmacological intervention, leading to the belief that they no longer need medication. This phenomenon can result in premature discontinuation and subsequent relapse. Conversely, patients who have experienced withdrawal symptoms in the past may be more anxious about medication discontinuation, leading to medication over-reliance (Figure 0.1).
- **Stigma and identity:** Long-term psychiatric medication use can sometimes conflict with a patient's self-concept. Some individuals feel that reliance on medication undermines their autonomy or resilience, whereas others may struggle with the stigma associated with psychiatric treatment. These factors can drive the desire to discontinue, even in cases where ongoing treatment remains beneficial.
- **Interpersonal influences:** Family members, friends, psychotherapists, other clinicians, and even social media influencers may play a role in reinforcing or discouraging medication use. Well-meaning but uninformed advice – such as "You've been doing great, maybe you don't need it anymore" – can inadvertently push patients towards stopping medication prematurely. Conversely, overly cautious or anxious caregivers, parents, or other family members may discourage discontinuation even when it is clinically appropriate.
- **Fear of dependence:** Although antidepressants, mood stabilizers, and stimulants do not induce physiological dependence in the same way as benzodiazepines, many patients nonetheless express concerns about "being on medication for life." This apprehension, rooted in a broader societal discomfort with psychiatric medications but also possibly related to cognitive factors (e.g., expectation of a negative or catastrophic reaction or long-term, irreversible side effects associated with continuing medication), can lead to discontinuation attempts driven more by emotional unease than by clinical necessity.

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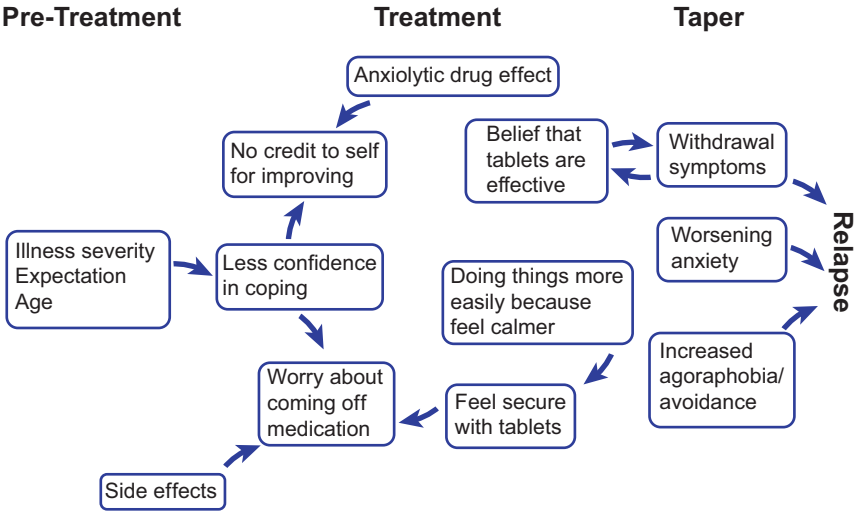


Figure 0.1 **Psychological factors affecting discontinuation of benzodiazepines.** Adapted from Başoğlu M, Marks IM, Kiliç C, Brewin CR, and Swinson RP. Alprazolam and exposure for panic disorder with agoraphobia: Attribution of improvement to medication predicts subsequent relapse. Br J Psychiatry 1994;164(5):652–659.

In a study examining psychological factors that affect benzodiazepine use, patients received 8 weeks of either alprazolam or placebo combined with therapy (either exposure or relaxation). When medication was tapered, patients who credited their improvement to medication experienced more severe withdrawal symptoms and a greater loss of therapeutic gains compared to those who attributed their progress to their own efforts. Several factors predicted external attributions to medication: baseline illness severity, older age, higher expectations from medication treatment, and more side effects during treatment. However, these factors did not predict relapse (Figure 0.1). The study underscores the importance of patient perceptions in (1) the long-term management of anxiety and (2) the success of deprescribing.

The Psychology of Stopping: Why It's Never Just about the Medication

By now, we appreciate that discontinuing medication isn't just about symptoms and side effects; it's about how patients, clinicians, and families think about medication. And these thoughts are shaped by personal experiences, cognitive biases, and emotional reactions rather than pure pharmacology. Patients might feel empowered and want to stop because they "don't need meds anymore," or they might fear stopping due to previously experienced withdrawal symptoms or a sense of dependence. Clinicians, on the other hand, often worry about relapse, liability, and the unpredictable nature of discontinuation. And then there's family – sometimes encouraging deprescribing, sometimes resisting it, often out of their own anxiety or experiences with the patient. These psychological factors create a tangle of expectations, fears, and assumptions that can either facilitate or sabotage deprescribing (Table 0.1).

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Table 0.1 How patients, clinicians, and family members think about stopping medication – why it's complicated and what drives their decisions

Factor	Patients	Clinicians	Family members
How people explain improvement	*"I feel better because of me, not the medication"* Patients may believe their recovery is due to personal strength, not the medication, making them more likely to stop	*"Stopping meds means relapse"* Many clinicians assume that stopping medication leads to worsening symptoms, making them hesitant to deprescribe *"Last time a patient stopped, it didn't go well … "* Past negative experiences stick in the clinician's mind	*If they stop, will everything fall apart?"* Families may assume that stopping medication means a return to crisis, making them push for continued treatment
Fear and anxiety	*Fear of being "dependent" on meds* Many patients feel uneasy about needing medication long term *Worry about withdrawal* If they've had bad discontinuation symptoms before, they may expect them again – even if a slow taper could prevent them	*Fear of relapse* Clinicians may overestimate the risks of stopping, leading them to continue medications out of caution rather than need *Legal and ethical concerns* Clinicians may fear blame if a patient relapses after stopping medication	*"What if stopping makes things worse?"* Even well-meaning family members can discourage deprescribing because of their own anxiety
Beliefs about medication	*"I don't want to be on this forever"* Some patients see long-term medication as a failure *"What if this is hurting me?"* Concerns about side effects – real or feared – often drive patients to stop medication	*"If it's working, why change it?"* Clinicians may not reassess medication once a patient is stable, even if deprescribing is reasonable or other factors have changed (e.g., patient has benefitted substantially from psychotherapy)	*"Medication is a safety net"* Families may see the medication as the only thing keeping their loved one well – even when deprescribing is reasonable

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Table 0.1 (cont.)

Factor	Patients	Clinicians	Family members
Expecting the worst (or the best)	*"If I stop, I'll have horrible withdrawal"* Patients may experience withdrawal just because they expect it (nocebo effect) *"If I stop, I'll be totally fine"* Overconfidence can also be a problem, leading to abrupt stopping and relapse	*"This is going to end badly"* Some clinicians expect tapering to fail before even trying *"I have to protect the patient from themselves"* Through a paternalistic lens, clinicians may discourage stopping even when it's a reasonable option	*"You did great, so you don't need meds anymore!"* Some family members encourage stopping too soon *"You're not well enough to stop"* Others push to stay on meds indefinitely
Social pressures and influence	*Advice from the internet, social media, peers, therapists or other clinicians* Patients may hear conflicting messages that shape their attitudes towards stopping *Family pressure* Sometimes loved ones push for stopping – or for continuing	*Guidelines vs. real-world experience* Clinicians juggle research findings, clinical instincts, and patient preferences when making deprescribing decisions. It is often difficult for clinicians to reconcile benefits demonstrated in short-term clinical trials with the acknowledgment that many psychiatric illnesses may require long-term maintenance. Added pressure may also come from managed care companies and pharmacy benefit managers	*"I just want them to be okay"* Family input can be helpful – or make the process even harder
Avoidance and safety behaviors	*Fear of discomfort leads to avoiding tapering altogether* Some patients never even try to stop because they're afraid of what might happen	*"Slow tapers are safer."* While generally true, some clinicians are so cautious that the process of deprescribing continues for an unnecessarily long period	*"Let's not rock the boat."* Families may resist change if things are going well

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Table 0.1 (cont.)

Factor	Patients	Clinicians	Family members
How past experiences shape beliefs	*If stopping went badly once, it must always go badly* Patients with past withdrawal or relapse often develop a learned fear of tapering *If stopping was easy once, it'll be easy again* The opposite is also true – some people underestimate the risks based on a single experience	*Clinicians remember the disasters more than the successes* A few bad experiences with stopping medication can make clinicians hesitant to deprescribe	*Family remembers the worst times* If they've seen their loved one struggle before, they may expect the worst from discontinuation

Tapering and Relapse Prevention

Discontinuing medication should almost always be a structured process rather than an abrupt event, except in situations where there is a severe reaction (e.g., neuroleptic malignant syndrome associated with an antipsychotic, Stevens–Johnson syndrome associated with lamotrigine). In general, the risk of discontinuation-emergent symptoms (e.g., withdrawal syndromes, rebound anxiety, and depressive relapse, rebound psychosis) is significantly reduced with gradual tapering. Patients must be counseled that discontinuation does not equate to failure and that a return to medication, if needed, is not an admission of weakness but rather a step in optimizing long-term mental health.

Yet, even when remission appears robust, discontinuation often reintroduces uncertainty. In a prospective study of individuals with remitted depression undergoing antidepressant discontinuation, more than one-third relapsed within six months, despite the absence of clinical, demographic, or neuropsychological predictors of relapse (Berwian et al., 2017). Even executive function and working memory measures, often regarded as markers of cognitive reserve, failed to differentiate those who remained well from those who relapsed. Although focused on depression, these findings raise broader concerns across psychiatric disorders in which discontinuation of medications with central neuroadaptive effects (e.g., SSRIs, benzodiazepines, antipsychotics) may unmask latent vulnerabilities that are not detectable during treatment. This clinical opacity underscores the need for carefully structured tapering strategies that acknowledge the invisible neural adjustments sustained during treatment and their potential reemergence during withdrawal.

Ultimately, the art of deprescribing is not simply about stopping medication but about ensuring the highest likelihood of sustained wellness. A thoughtful, patient-centered approach – incorporating clinical, biological, and psychological factors – maximizes the probability of a successful transition, whether that means continuing, tapering, switching, or discontinuing medication altogether.

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The Neurobiology of Medication Withdrawal

Withdrawal from psychotropic medications is not merely a function of drug half-life or dose reduction (although these are very important) but rather a neurobiological process driven by both homeostatic and allostatic mechanisms (Table 0.2). Chronic exposure to psychotropic agents perturbs neurobiological homeostasis, triggering allostatic adaptations – including compensatory changes in receptor density, synaptic transmission, intracellular signaling cascades, and neurotransmitter regulation. These adaptations allow the brain to function in the presence of the drug, but they come at a cost: when the drug is discontinued, the CNS – now recalibrated to a new "set point" – must re-establish homeostasis in the absence of the drug. This process is neither immediate nor seamless and may produce withdrawal syndromes that range from mild discomfort to severe rebound. The severity of withdrawal reflects the extent of allostatic load accrued during chronic medication use. Understanding the molecular and neurophysiological underpinnings of medication withdrawal is essential for optimizing tapering strategies, mitigating withdrawal-related distress, and minimizing the risk of prolonged dysregulation.

Benzodiazepines

Benzodiazepines enhance GABAergic inhibition by binding to gamma-aminobutyric acid A ($GABA_A$) receptors, increasing chloride influx, hyperpolarizing neurons, and reducing neuronal excitability. While this mechanism underlies their anxiolytic, sedative, and anticonvulsant properties, chronic benzodiazepine use leads to homeostatic adaptations that attempt to restore baseline neural activity. These changes include $GABA_A$ receptor downregulation, altered receptor trafficking, and secondary effects on dopaminergic and serotonergic systems, all contributing to the withdrawal syndromes upon discontinuation. Thus, when benzodiazepines are abruptly stopped, these adaptations produce rebound hyperexcitability, manifesting as anxiety, insomnia, autonomic instability, and, in severe cases, seizures (Figure 0.2). Further, increased dopaminergic activity during withdrawal may contribute to agitation and perceptual disturbances, while serotonergic dysregulation can exacerbate emotional lability and further contribute to rebound anxiety (Figure 0.2).

Table 0.2 Homeostasis, neuroadaptation, and allostasis in medication withdrawal

Homeostasis	Maintains baseline neurotransmitter levels before drug exposure	Seeks to restore balance after drug discontinuation
Allostasis	Adaptively changes receptor density, signaling pathways, and neurotransmitter production to maintain function in the presence of the drug	Requires time to recalibrate as the system "unlearns" drug-dependent adaptations
Neuroadaptation	Brain adjusts to chronic drug presence, shifting its set points	Abrupt discontinuation forces rapid re-equilibration, leading to withdrawal symptoms
Allostatic load	Accumulates over prolonged drug exposure (e.g., magnitude of receptor blockade or enzyme inhibition) as the brain compensates for pharmacological effects	Greater load predicts more severe withdrawal and prolonged dysregulation

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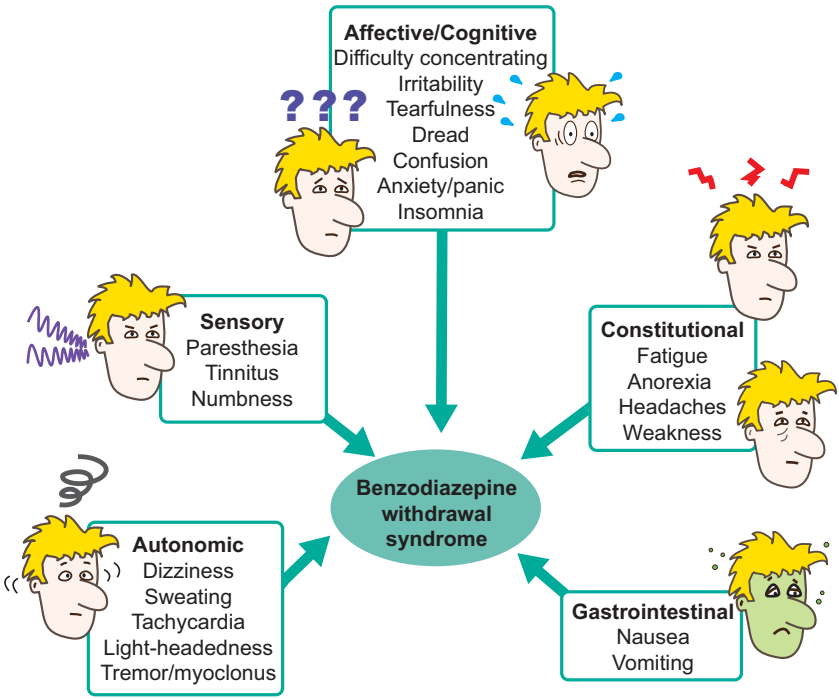


Figure 0.2 **Benzodiazepine withdrawal.** Benzodiazepine withdrawal often represents a full-body rebound of hyperexcitability, affecting multiple systems. Withdrawal is not just a reversal of benzodiazepine effects – it's a neurobiological rebound that can be severe, prolonged, and distressing.

$GABA_A$ Receptor Adaptations: Downregulation and Receptor Sequestration

Prolonged benzodiazepine exposure induces use-dependent neuroadaptive changes in $GABA_A$ receptor regulation. These adaptations represent a sequence of compensatory mechanisms that counteract excessive inhibitory signaling:

1. **Desensitization (tachyphylaxis):** With continued benzodiazepine use, $GABA_A$ receptors become less responsive to both endogenous GABA and exogenous benzodiazepines. This desensitization manifests as tolerance and, based on single-photon emission computerized tomography (SPECT) studies in humans, relates to uncoupling in which $GABA_A$/benzodiazepine receptors are no longer functionally connected to their associated signaling pathways, despite being present in the brain (Fujita et al., 1999).
2. **Receptor sequestration (endocytosis):** To reduce excessive inhibitory signaling, neurons internalize $GABA_A$ receptor subunits via endocytosis (Figure 0.3), effectively removing receptors from the synaptic membrane. This process uncouples the allosteric interaction between GABA and the benzodiazepine binding site, rendering the receptor less sensitive to benzodiazepine modulation.
3. **Receptor degradation and reduced gene expression:** Over time, internalized receptor subunits undergo lysosomal degradation (Figure 0.3, central panel), decreasing the total number of functional $GABA_A$ receptors. Simultaneously, gene expression of receptor subunits is repressed, further limiting receptor synthesis, which occurs over the first several days to weeks of treatment (Figure 0.4) and compounding tolerance (Fijita et al., 1999).

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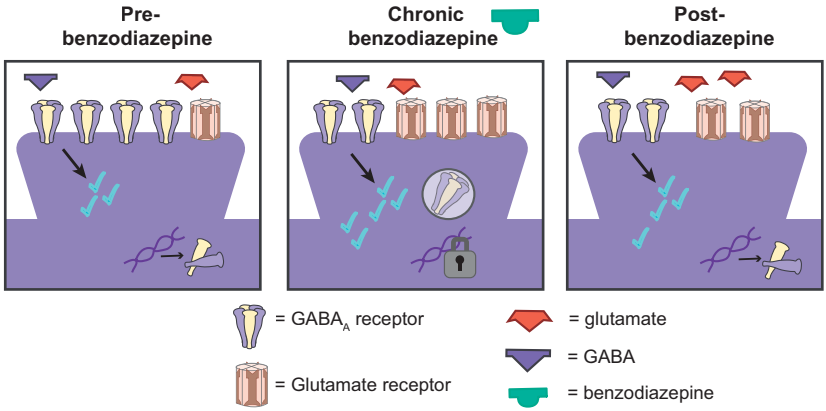


Figure 0.3 **Neurobiology of chronic benzodiazepine treatment and withdrawal.** Following administration of a benzodiazepine, GABA$_A$ receptors (purple and cream) are downregulated and glutamate receptors (brown and tan) are upregulated. The GABA$_A$ receptors later become less sensitive because of allosteric uncoupling between GABA and the benzodiazepine binding site. Chronic benzodiazepine use (central panel) also decreases GABA$_A$ subunit expression (padlock) and increases endocytosis (and subsequent degradation) of GABA$_A$ receptors (purple and cream receptor inside circle). In the right panel, these cellular changes, including persistent decreased GABA$_A$ receptor expression and hyperexcitability to glutamate, drive benzodiazepine withdrawal symptoms.

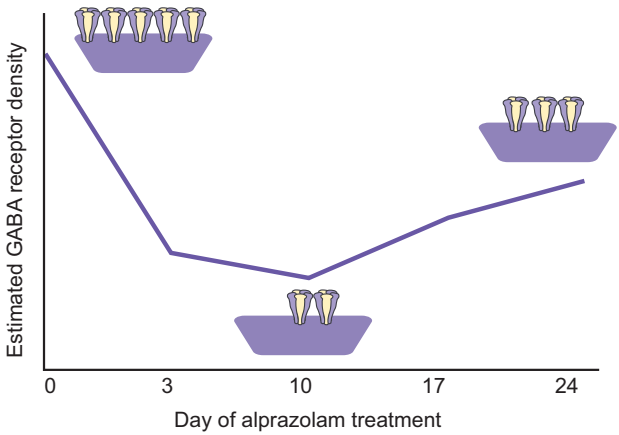


Figure 0.4 **Changes in GABA$_A$ receptor density during benzodiazepine treatment.** Changes of benzodiazepine receptors during chronic benzodiazepine administration in humans. Adapted from Fujita M, Woods SW, Verhoeff NPLG, et al. Changes of benzodiazepine receptors during chronic benzodiazepine administration in humans. Eur J Pharmacol 1999;368(2–3):161–172.

Interestingly, unlike barbiturates or neurosteroids, benzodiazepines often induce receptor desensitization and sequestration without significantly reducing overall receptor numbers, suggesting a nuanced form of receptor plasticity that may explain the rapid return of function upon discontinuation.

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Neurobiology of Benzodiazepine Withdrawal

When benzodiazepines are withdrawn after prolonged use, the GABAergic system – now downregulated and desensitized – fails to provide its usual inhibitory tone. At the same time, excitatory neurotransmission, which had been suppressed by chronic benzodiazepine exposure, rebounds aggressively, leading to a state of cortical hyperexcitability.

1. **Reduced GABAergic inhibition:** With fewer functional $GABA_A$ receptors (Figure 0.3) and decreased GABA sensitivity, inhibitory tone is lost, allowing for uncontrolled excitatory neurotransmission.
2. **Upregulation of excitatory NMDA receptors:** In response to prolonged inhibition, glutamatergic N-methyl-D-aspartate (NMDA) receptors are upregulated (Figure 0.3), further exacerbating hyperexcitatory signaling upon benzodiazepine withdrawal. This increased excitatory drive may contribute to seizures, tremors, autonomic dysregulation, and perceptual disturbances.
3. **Rebound anxiety:** The loss of GABAergic suppression of the amygdala and hypothalamic–pituitary–adrenal axis leads to exaggerated stress responses, panic attacks, and, in cases of severe withdrawal, autonomic instability.

Benzodiazepine Effects on Monoaminergic Systems

While benzodiazepines exert their primary effects through GABAergic modulation, they also produce profound secondary changes in dopaminergic and serotonergic neurotransmission, particularly in reward, motivation, and mood regulation. These effects become particularly relevant in withdrawal, as dopaminergic and serotonergic deficits contribute to post-withdrawal anhedonia, dysphoria, and affective instability.

Dopaminergic neurons in the ventral tegmental area (VTA), which project to the nucleus accumbens (reward system) and prefrontal cortex, are tonically inhibited by GABAergic interneurons (Figure 0.5). Benzodiazepines enhance GABAergic inhibition of these interneurons, thereby reducing their suppression of VTA dopamine neurons. This paradoxically increases dopamine neuron firing (Figure 0.5) and enhances dopamine release in the nucleus accumbens, contributing to benzodiazepine-induced mood effects and reinforcing properties.

However, with chronic use, the dopaminergic system adapts. Specifically, D_2 receptor downregulation in the nucleus accumbens attenuates dopaminergic signaling, contributing to tolerance. And reduced baseline dopamine neuron firing (Figure 0.5) blunts reward responses and, over time, dampens the ability to experience pleasure.

Upon withdrawal, the sudden loss of benzodiazepine-mediated stimulation of dopamine release (Figure 0.5) ultimately decreases its release, which may lead to anhedonia, dysphoria, and motivation. Also, this may accentuate stress reactivity as dopamine modulation of stress circuits in the prefrontal cortex and limbic system becomes dysregulated.

Benzodiazepines also modulate the serotonergic system (Lima et al., 1993), primarily by inhibiting serotonergic neurons in the dorsal raphe nuclei, decreasing their firing rates, and decreasing $5\text{-}HT_{1A}$ expression in the raphe (Lima et al., 1993). GABAergic interneurons in the raphe tonically inhibit serotonergic neurons, and benzodiazepines enhance this inhibition, thereby reducing serotonin release in cortical and limbic regions.

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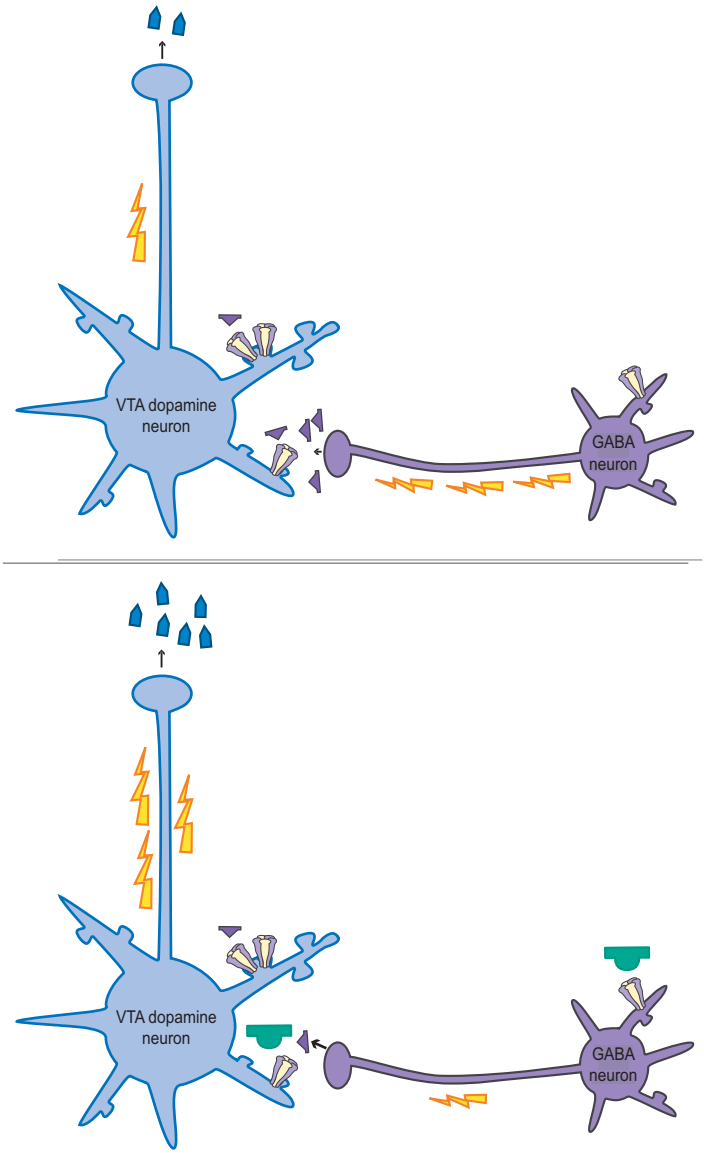


Figure 0.5 **GABA regulates dopamine release in the ventral tegmental area (VTA).** The activity of dopaminergic neurons (blue) in the VTA is influenced by tonic GABAergic tone (purple neuron). In the bottom panel, benzodiazepine administration (green polygon) increases the inhibitory effect on these dopaminergic neurons, increasing their firing (lightning symbol) and subsequent dopamine (blue pentagon) release. However, during benzodiazepine withdrawal (top panel), the firing frequency of the inhibitory GABA neuron increases, which subsequently decreases the activity of the dopaminergic neuron (blue) and then reduces dopamine (blue pentagon) release.

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While this effect contributes to acute anxiolysis, chronic benzodiazepine use reduces serotonergic tone. Upon benzodiazepine withdrawal, (1) serotonin release remains suppressed, potentially contributing to depressive symptoms, rebound anxiety, and irritability and (2) disrupted serotonergic modulation of REM sleep leads to rebound insomnia, vivid dreams, and nighttime awakening.

Thus, benzodiazepine withdrawal not only affects GABAergic systems but also disrupts serotonin-dependent emotional regulation and sleep–wake cycles (Rickels et al., 1990).

Orexin Receptor Antagonists

Orexin receptor antagonists facilitate sleep by blocking orexin signaling in the lateral hypothalamus, thereby suppressing wake-promoting neurons. Orexin neurons, located in the hypothalamus, exert excitatory effects on the locus coeruleus (noradrenergic), raphe nuclei (serotonergic), and tuberomammillary nucleus (histaminergic), all of which contribute to wakefulness. Chronic suppression of these pathways may upregulate orexin receptors as the brain responds to the pharmacologically induced inhibition of wakefulness.

Rebound effects may occur upon discontinuing orexin receptor antagonists, although this has not been consistently observed in studies or clinical trials. That said, upregulated orexin receptors could ostensibly become excessively responsive to orexin, leading to rebound insomnia, increased nocturnal awakenings, and heightened sleep fragmentation. Additionally, the loss of orexin blockade results in the disinhibition of locus coeruleus activity, leading to enhanced noradrenergic firing and increased physiological arousal. Patients may have trouble falling asleep, experience prolonged sleep latency, and an overall decrease in sleep efficiency following withdrawal.

In some, but not all, studies, this sleep disruption may persist for several nights, depending on the duration of prior treatment. The neurobiological recalibration process involves a gradual downregulation of orexin receptor density and normalization of wake–sleep circuitry.

Beta Blockers

Beta blockers antagonize beta-1- and beta-2-adrenergic receptors, reducing the physiological effects of catecholamines (e.g., norepinephrine and epinephrine). Over time, the chronic blockade of these receptors induces compensatory receptor upregulation as the system attempts to maintain adrenergic responsiveness despite the pharmacological inhibition. The result is an increased density of beta-adrenergic receptors (Golf and Hansson, 1986), heightened adenylate cyclase activity, and an overall sensitization of the sympathetic nervous system.

When beta blockers are discontinued abruptly, the previously suppressed catecholaminergic system becomes hyperactive, leading to rebound tachycardia, palpitations, increased blood pressure, tremor, and anxiety. The surge in sympathetic outflow is driven by both excessive norepinephrine release and an exaggerated postsynaptic receptor response due to receptor upregulation.

In patients with underlying cardiovascular pathology (e.g., hypertension or arrhythmias), beta-blocker withdrawal can precipitate hypertensive crises or angina due to sudden adrenergic overactivity, although this has not been observed in all studies. To mitigate these risks, a slow tapering strategy may allow for the gradual downregulation of beta-adrenergic receptor density and a controlled re-equilibration of autonomic function.

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Alpha-2 Agonists

Alpha-2-adrenergic agonists, including clonidine and guanfacine, exert their effects by stimulating presynaptic alpha-2 autoreceptors, leading to reduced norepinephrine release and decreased sympathetic outflow. With long-term use, the locus coeruleus adapts to this persistent suppression by downregulating inhibitory alpha-2 receptor sensitivity and increasing norepinephrine synthesis.

SSRIs

Selective serotonin reuptake inhibitors (SSRIs) inhibit the serotonin transporter (SERT), prolonging serotonin signaling in brain regions involved in mood regulation, such as the prefrontal cortex, hippocampus, and limbic structures. However, chronic SSRI exposure induces widespread neuroadaptive changes beyond acute serotonin reuptake inhibition (Barton and Hutson, 1999). These effects reshape serotonergic neurotransmission through altered receptor expression, synaptic physiology, and effects on other monoaminergic systems. These adaptations – while crucial for the therapeutic effects of SSRIs – also contribute to withdrawal syndromes when the medication is discontinued.

Functional neuroimaging adds yet another layer to our understanding of SSRI discontinuation, showing not just what happens at the molecular level, but what the brain does in response to withdrawal. In a longitudinal fMRI study, Erdmann et al. (2024) observed that amygdala reactivity to negative emotional stimuli increased following SSRI discontinuation, but only in patients who later relapsed. While antidepressants appear to constrain the amygdala's responsiveness and effectively lower the "gain" on emotional threat processing, discontinuation seems to lift this constraint, priming the system for reactivity and potentially for relapse. In this study, the increase in amygdala reactivity occurred before symptoms returned, suggesting that the neural signature of relapse may emerge before its clinical appearance, and that antidepressant discontinuation itself reactivates affective circuitry that had been stabilized during treatment (Erdmann et al., 2024).

Chronic SSRI Exposure and Neuroadaptive Changes

One of the most well-characterized adaptations to long-term SSRI treatment is downregulation of SERT expression (Abumaria et al., 2014; Benmansour et al., 1999) (Figure 0.6). In response to persistent serotonin reuptake blockade, the brain reduces the number of SERT proteins available. This compensatory mechanism maintains serotonergic homeostasis. However, when the SSRI is removed, this downregulated transporter system may be unable to rapidly restore serotonin homeostasis, leading to abrupt shifts in synaptic serotonin (Figure 0.6).

In addition to changes in SERT expression, serotonin receptor function/expression shifts with chronic SSRI use (Figure 0.6). Presynaptic 5-HT_{1A} autoreceptors, which regulate serotonin release via negative feedback inhibition, become hypersensitive when SSRIs are withdrawn (Collins et al., 2024). This increased sensitivity means that discontinuation not only removes reuptake inhibition but also leads to excessive serotonin release as the neuron also becomes hyperexcitable (Collins et al., 2024), contributing to rebound anxiety, dysphoria, and other withdrawal symptoms.

Further, SSRIs modulate expression of 5-HT_{2A} receptors, a subtype involved in excitatory serotonergic neurotransmission. Chronic 5-HT_{2A} antagonism enhances slow-wave sleep, reduces nighttime arousals, and modulates cortical excitability. When SSRIs are discontinued, a 5-HT_{2A} rebound effect may potentially lead to increased wakefulness, REM sleep fragmentation, and heightened sensory sensitivity – factors that contribute to withdrawal-related insomnia and dysasthesias.

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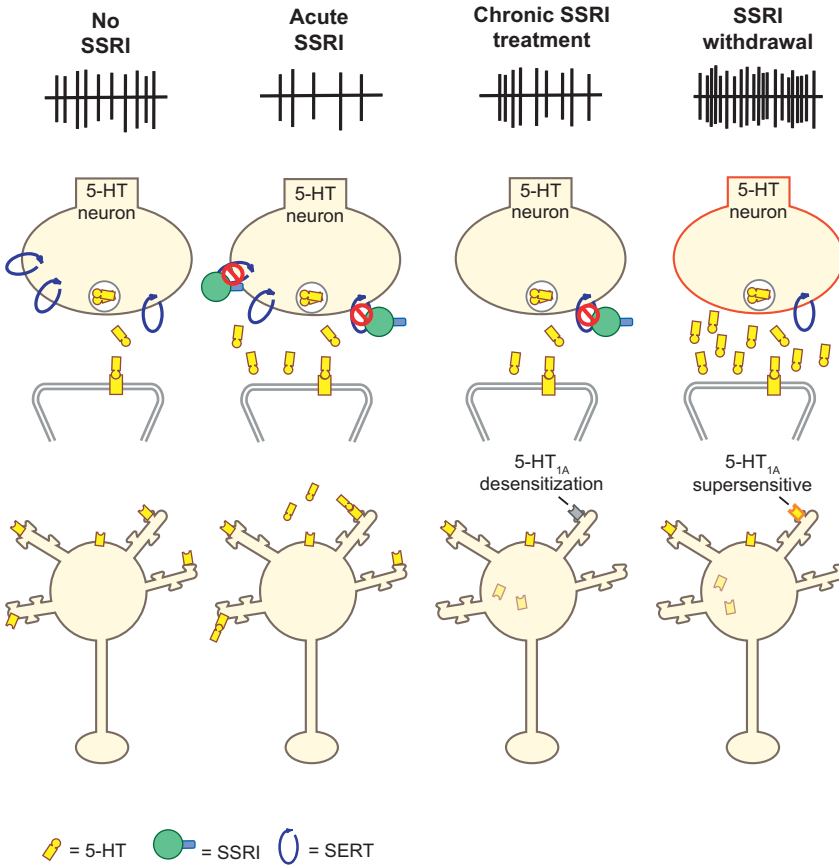


Figure 0.6 **Selective serotonin reuptake inhibitor (SSRI) initiation and withdrawal.** SSRIs initially reduce serotonergic neuron firing due to increased activation of 5-HT_{1A} autoreceptors, which undergo internalization over time. Concurrently, serotonin transporter (SERT) inhibition increases extracellular serotonin (5-hydroxytryptamine; 5-HT), though clinical effects are delayed due to autoreceptor regulation. With chronic SSRI administration, 5-HT_{1A} autoreceptors become desensitized, leading to sustained serotonergic transmission, while SERT undergoes internalization and degradation, reducing reuptake capacity. Upon discontinuation, serotonergic neuron firing rates increase and the neuron becomes "hyperresponsive," resulting in a surge of synaptic 5-HT. This rebound effect is accompanied by increased neuronal excitability of serotonergic neurons and supersensitivity of 5-HT_{1A} and postsynaptic 5-HT receptors, contributing to withdrawal-related anxiety-like symptoms and other withdrawal symptoms.

Beyond Serotonin: Monoaminergic Crosstalk and Dopaminergic/Noradrenergic Involvement

Chronic SSRI administration influences dopaminergic and noradrenergic systems:

- **Dopamine:** Serotonergic pathways interact with dopaminergic circuits, particularly in the mesolimbic and mesocortical systems, which are involved in motivation, reward processing, and emotional regulation. Chronic SSRI exposure may indirectly enhance dopamine release, particularly in the prefrontal cortex, through serotonin-mediated inhibition of GABAergic interneurons
- **Norepinephrine:** In preclinical studies, most SSRIs increase extracellular norepinephrine concentrations, including in subcortical areas (Kitaichi et al.,

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2004). Specifically, 5-HT neurons may – through direction connections – inhibit noradrenergic neurons in the locus coeruleus by decreasing their firing frequency (Szabo et al., 2000). Finally, SSRIs with activity at the norepinephrine transporter (NET) may also affect locus coeruleus activity by modulating alpha-2-adrenergic autoreceptor sensitivity

When certain SSRIs are discontinued abruptly, the balance between serotonin, dopamine, and norepinephrine rapidly shifts, leading to diffuse neurotransmitter disequilibrium.

Neurobiology of SSRI Discontinuation and Withdrawal Syndromes

SSRI withdrawal is characterized by altered extracellular serotonin in some preclinical studies, occurring as a result of simultaneous loss of reuptake inhibition and excessive 5-HT_{1A} autoreceptor-mediated suppression of serotonin release (Sharp et al., 1997).

Among the most distinctive SSRI withdrawal phenomena are neurological and dysasthesias (i.e., "brain zaps"). These sensations – described as brief, electrical shock-like sensations in the brain – are believed to result from dysregulated serotonin signaling within cortical and thalamic circuits, combined with abnormal glutamatergic activity following the loss of serotonergic modulation.

Additionally, abrupt SSRI discontinuation triggers compensatory adrenergic and cholinergic rebound effects, leading to autonomic symptoms including dizziness, nausea, and sweating, as well as other symptoms such as sleep disturbances (Michelson et al., 2000). The rapid resensitization of 5-HT_{2A} receptors further contributes to disrupted REM sleep, which may produce nighttime awakenings, intense dreams, and insomnia.

Finally, withdrawal severity is influenced by multiple factors, including SSRI half-life, SERT occupancy, and individual neurochemical variability (Davies and Read, 2019), which are discussed within the individual drug monographs. Shorter-acting agents, such as paroxetine and fluvoxamine, produce more pronounced withdrawal effects (Davies and Read, 2019; Fava and Cosci, 2019; Fava et al., 2015) due to their rapid elimination and loss of SERT occupancy, while longer-acting agents, such as fluoxetine, may not produce as intense withdrawal sydromes.

Findings from meta-analyses reinforce and contextualize the neurobiological mechanisms underlying SSRI withdrawal (Kalfas et al., 2025). In a systematic review of 49 randomized trials including over 17,000 participants, abrupt discontinuation of antidepressants was associated with a small but measurable increase in symptoms at one week (on average, one additional symptom compared to placebo or continued treatment) with most symptoms resolving by the second week (Kalfas et al., 2025). The most commonly reported symptoms (dizziness, nausea, anxiety, and insomnia) closely align with serotonergic, adrenergic, and cholinergic rebound phenomena. Dizziness may reflect disrupted serotonergic modulation of brainstem and vestibular circuits; nausea likely arises from serotonergic withdrawal in the enteric nervous system. Anxiety and agitation, which were observed more frequently than mood symptoms, are consistent with 5-HT_{1A} autoreceptor–mediated suppression of serotonergic tone and downstream disinhibition of limbic pathways. Autonomic symptoms such as sweating and sleep disruption may reflect compensatory cholinergic and adrenergic overactivity. Together, these data support the view that withdrawal is a time-limited neurochemical response (Kalfas et al., 2025).

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SNRIs

Serotonin–norepinephrine reuptake inhibitors (SNRIs) share many withdrawal characteristics with SSRIs but introduce additional noradrenergic withdrawal effects due to their inhibition of the NET.

Chronic SNRI exposure downregulates NET and reduces norepinephrine clearance and increases synaptic norepinephrine availability. Additionally, presynaptic alpha-2-adrenergic autoreceptors, which regulate norepinephrine release, become desensitized by prolonged exposure to elevated norepinephrine levels (Figure 0.7). Upon discontinuation, NET function rebounds, leading to rapid shifts in synaptic norepinephrine, while desensitized alpha-2 autoreceptors fail to properly regulate norepinephrine release. This results in sympathetic overactivation (e.g., palpitations, sweating, dizziness, and blood pressure fluctuations). Accordingly, patients discontinuing SNRIs often report panic, autonomic instability, and increased emotional volatility, reinforcing the need for slower dose reductions to allow NET and adrenoreceptor recalibration.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are among the most pharmacologically complex antidepressants, modulating multiple neurotransmitter systems simultaneously. Their therapeutic effects stem primarily from serotonin and norepinephrine reuptake inhibition, but TCAs also have anticholinergic, antihistaminergic, and alpha-adrenergic blocking properties. This diverse receptor profile contributes to their efficacy but also means that discontinuation is accompanied by a spectrum of withdrawal symptoms.

Neuroadaptations during Chronic TCA Use

Prolonged TCA exposure leads to adaptive changes in synaptic function, receptor expression, and intracellular signaling pathways. These adaptations occur across mono-

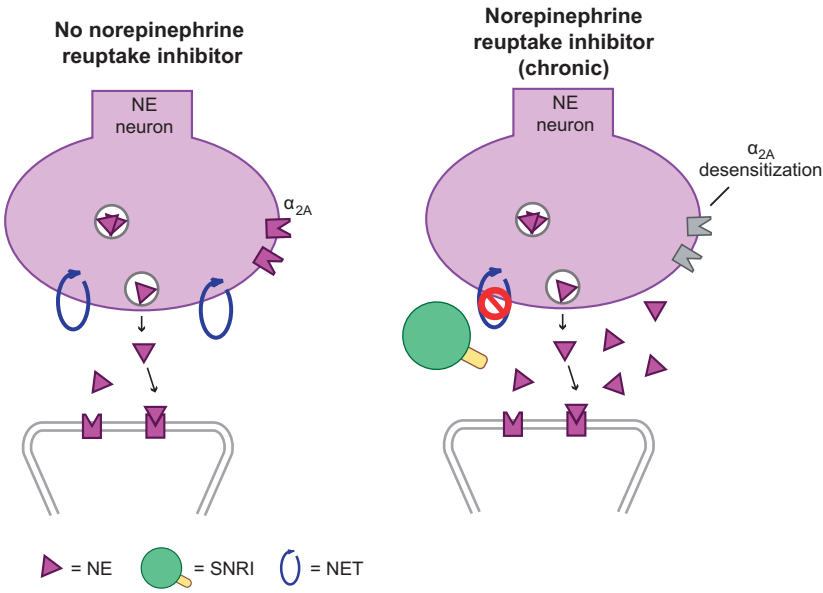


Figure 0.7 **Changes associated with chronic serotonin–norepinephrine reuptake inhibitor (SNRI) use.** With chronic SNRI use, there is desensitization of alpha-2A (α_{2A}) receptors and a decrease in norepinephrine transporter (NET) availability.

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aminergic, cholinergic, and histaminergic systems, each contributing uniquely to withdrawal when the medication is discontinued.

Monoaminergic Adaptations: Serotonin and Norepinephrine Dysregulation

Like SSRIs and SNRIs, TCAs inhibit SERT and NET, shifting synaptic concentrations of serotonin and norepinephrine (Figure 0.8) (Zhao et al., 2008). Over time, the brain attempts to compensate for this altered monoaminergic neurotransmission by downregulating SERT and NET expression (Zhao et al., 2008); TCAs also reduce NET density and expression (Zhao et al., 2008; Zhu et al., 1998; Zhu et al., 2002) (Figure 0.8), leading to prolonged norepinephrine activity and desensitization of alpha-2-adrenergic autoreceptors, which normally regulate norepinephrine release.

Several (although not all) studies suggest that TCAs decrease NET messenger RNA (mRNA) within the first 3 days of treatment and reduce NET numbers within 1–3 days. Further, NET mRNA remains stable after 1 day of TCA exposure but by the third day of treatment mRNA production decreases. Beyond transcriptional regulation, TCAs also redistribute NET away from the plasma membrane (Pan et al., 2002), limiting functional transporter availability. This NET internalization is unaffected by kinase and phosphatase inhibitors (Pan et al., 2002), suggesting a distinct regulatory mechanism. It has also been hypothesized that TCA blockade of NET may serve as a "nonfunctional tag," triggering NET internalization and recycling. This turnover, though necessary for transporter replacement, likely explains the lag in NET recovery post-TCA withdrawal (Mandala and Ordway, 2006).

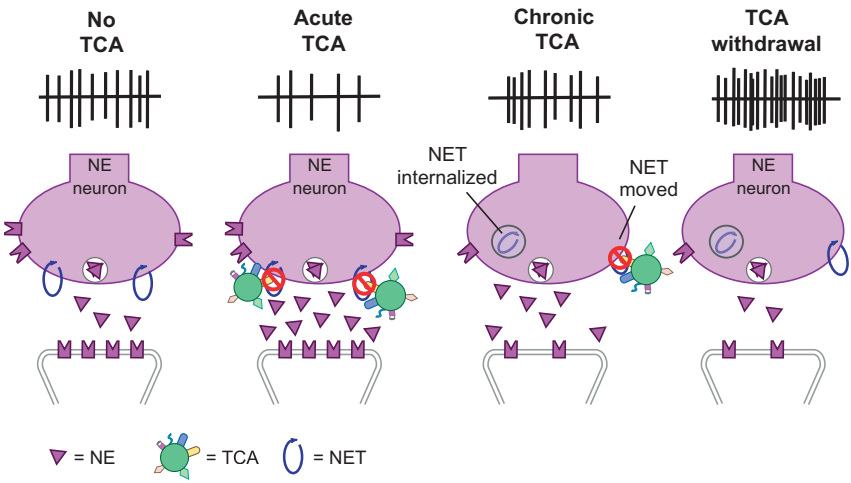


Figure 0.8 **Changes with acute, chronic, and withdrawn tricyclic antidepressant (TCA) treatment.** From left to right: In the absence of TCAs, norepinephrine (purple triangles) is released from the presynaptic neuron (purple) and cleared via the norepinephrine transporter (NET). Acute TCA (green circle) administration blocks NET, increasing synaptic norepinephrine levels and enhancing noradrenergic signaling. Over time, chronic TCA treatment induces compensatory neuroadaptive changes, including downregulation of postsynaptic receptors and downregulation of NET expression and internalization of NET. Upon TCA withdrawal, NET activity remains enhanced. At the same time, receptor sensitivity is still dampened, leading to a transient noradrenergic deficiency state and potential withdrawal symptoms such as rebound depression, anxiety, and autonomic symptoms.

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Finally, when TCAs are abruptly discontinued, NETs remain downregulated (Figure 0.8), leading to a sudden shift in synaptic norepinephrine (Charney et al., 1982). In fact, following TCA withdrawal, NET binding and receptor levels recover gradually over several days to a week (Mandela and Ordway, 2006). This likely contributes to depressed mood, anhedonia as well as fatigue, flu-like symptoms, and anxiety due to dysregulated signaling. Additionally, withdrawal may exacerbate noradrenergic rebound (Charney et al., 1982), causing irritability, restlessness, and increased heart rate as the locus coeruleus – previously suppressed by enhanced norepinephrine signaling – becomes hyperactive.

Anticholinergic Rebound: Receptor Supersensitivity and Cognitive Symptoms

Many TCAs, especially amitriptyline, imipramine, and doxepin, produce strong muscarinic acetylcholine (mACh) receptor antagonism. Chronic blockade of mACh receptors (M_1–M_5) leads to (1) compensatory upregulation of postsynaptic mACh receptors to maintain cholinergic tone and (2) increased synthesis and release of acetylcholine (ACh) to overcome persistent muscarinic inhibition. Then, when a TCA with strong anticholinergic activity is discontinued, the sudden loss of receptor blockade leads to cholinergic rebound, characterized by:

- Rebound hypersalivation, nausea, diarrhea, and sweating, as muscarinic receptor overactivity affects autonomic function
- Increased muscle tension and restlessness, due to cholinergic dysregulation in motor circuits
- Cognitive "fog," difficulty concentrating, and memory impairment, resulting from rebound hyperactivity in the hippocampus and prefrontal cortex, where cholinergic neurons play a crucial role in executive function

Histaminergic Rebound

Several TCAs, including doxepin and amitriptyline, have strong H_1 histamine receptor antagonism, contributing to their sedative and sleep-promoting effects. Prolonged histamine receptor blockade upregulates H_1 receptors, decreases histamine synthesis, and, upon discontinuation, results in histaminergic rebound. Because histamine plays a role in appetite regulation, some patients may also experience appetite or weight changes during TCA withdrawal.

Alpha-Adrenergic Dysregulation

TCAs antagonize alpha-1-adrenergic receptors, leading to chronic suppression of sympathetic tone and compensatory receptor upregulation. Upon discontinuation, vasomotor instability occurs (e.g., dizziness and blood pressure fluctuations), as vascular alpha-1 receptors are hypersensitive to circulating norepinephrine. Tachycardia and palpitations may develop due to loss of adrenergic inhibition in cardiac control centers. However, some of these effects may be influenced by developmental factors. For example, in children, alpha-1-adrenergic antagonism produces different side effects compared to adults due to age-dependent shifts in blood pressure regulation. Younger children rely more on cardiac output (heart rate times stroke volume) to maintain blood pressure, whereas adolescents and adults increasingly depend on peripheral vascular resistance. As a result, alpha-1 blockade in younger children (ages 6–12) may cause less reflex tachycardia, while in adolescents (ages 12–18), where peripheral vascular resistance plays a greater role, side effects (and withdrawal effects) become more consistent with what is typically observed in adults where vasoconstriction is more important for blood pressure maintenance.

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Autonomic rebound symptoms (e.g., sweating, flushing, and thermoregulatory instability) can emerge as sympathetic outflow fluctuates (Charney et al., 1982). These effects are most pronounced in TCAs with strong alpha-1 antagonism, such as amitriptyline and doxepin, and are exacerbated by abrupt discontinuation.

Mixed Dopamine–Serotonin Receptor Antagonists

Second-generation antipsychotics (SGAs) have broad neuropharmacological effects, modulating dopaminergic, serotonergic, histaminergic, and adrenergic systems. The withdrawal syndromes associated with discontinuation are similarly complex, reflecting compensatory adaptations that develop over time. Key neurobiological changes during withdrawal include dopaminergic supersensitivity, histaminergic resensitization, serotonin receptor rebound effects, and disturbances in sleep architecture. Additionally, withdrawal dyskinesias – characterized by abnormal involuntary movements – can emerge due to delayed dopaminergic regulation.

Dopaminergic Supersensitivity

SGAs produce their antipsychotic effects through D_2 receptor blockade, reducing dopaminergic neurotransmission in the mesolimbic and mesocortical pathways and this is thought to relate to a series of "supersensitivty"-related phenomena (Kruyer et al., 2021). However, chronic blockade does more than just suppress dopamine – it reshapes the system, rewiring neural circuits in ways that become particularly problematic upon withdrawal. Clusters of D_2-containing neurons in the striatum (specifically medium spiny neurons) are hyperactivated during chronic antipsychotic treatment, after discontinuation, and in response to external stimuli (Santa et al., 2023). This hyperactivity, a downstream effect of chronic dopamine suppression, contributes to the behavioral and motor symptoms of antipsychotic withdrawal.

Chronic D_2 receptor blockade leads to decreases in dopamine transporter (DAT) expression (Nikolaus et al., 2009) and D_2 receptor upregulation (Schroder et al., 1998; Varela et al., 2014), as postsynaptic neurons attempt to maintain dopaminergic signaling (Figure 0.9). But it's not just about receptor numbers. It's about circuit-level dysregulation. The loss of modulatory dopaminergic input leaves D_2-containing neurons hyperexcitable, with glutamatergic drive taking over in the absence of normal dopamine modulation (Santa et al., 2023). Further complicating this picture, 5-HT_{2A} receptors – key modulators of dopamine release – undergo region-specific changes, with decreased density in the prelimbic cortex and nucleus accumbens but increased expression in the caudate-putamen (Charron et al., 2015). These shifts in 5-HT_{2A} receptor density amplify dopamine supersensitivity and increase the risk of withdrawal-related hyperdopaminergic states. This increase in D_2 receptor density and sensitivity occurs gradually but becomes problematic when the drug is discontinued.

Upon withdrawal, the sudden loss of D_2 receptor antagonism allows excess dopamine release to flood hypersensitive receptors, leading to a hyperdopaminergic state (Figure 0.9). However, this oversimplifies the mechanism: what drives behavioral supersensitivity is the interplay between dopamine insensitivity, glutamate hyperresponsiveness, and 5-HT-mediated modulation of dopamine release (Charron et al., 2015; Santa et al., 2023).

Withdrawal dyskinesia, a movement disorder that emerges following the abrupt discontinuation or rapid tapering of antipsychotics, is distinct from tardive dyskinesia. Unlike tardive dyskinesia, which results from chronic D_2 receptor blockade leading to long-term receptor supersensitivity, withdrawal dyskinesia is a transient hyperki-

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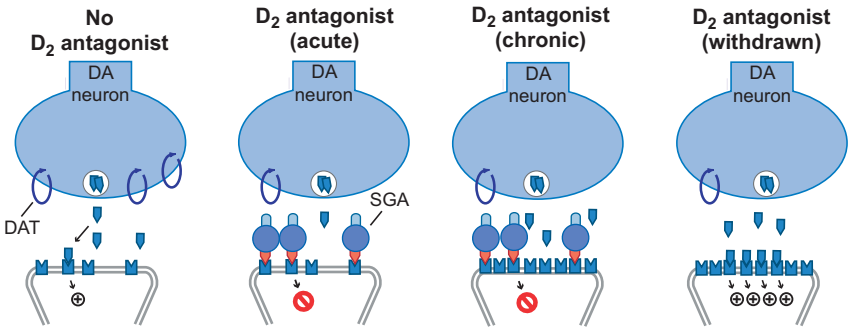


Figure 0.9 **Acute effects of dopamine antagonists and the consequences of their withdrawal, focusing on dopamine transporters (DATs) and D_2 receptors.** Baseline dopamine function (far left): In the normal state, dopamine (blue hexagons) is stored in vesicles, released into the synapse, and binds to dopamine receptors. Excess dopamine is cleared by reuptake through the DAT or enzymatic degradation. Acutely, dopamine antagonists block postsynaptic D_2 receptors. The presynaptic neuron continues releasing dopamine, but its effects are diminished, leading to compensatory increases in dopamine release. Then, with prolonged dopamine blockade (third panel), the neuron adapts by upregulating D_2 receptors. The presynaptic neuron may also increase dopamine release, but the blockade at postsynaptic receptors persists. When the antagonist is suddenly withdrawn (far right), the now upregulated D_2 receptors are exposed to excessive dopamine, leading to D_2 supersensitivity. This results in excessive DA signaling, contributing to withdrawal symptoms (e.g., agitation, dyskinesias, and rebound psychosis).

netic movement disorder that occurs due to acute dysregulation of dopaminergic tone in the basal ganglia. As before, this withdrawal state reflects a maladaptive shift in the balance of dopaminergic, glutamatergic, and serotonergic inputs, with hyperexcitable D_2-containing striatal neurons amplifying motor instability and serotonin-mediated modulation influencing dopamine reactivity.

In sum:

- **D_2 receptor hypersensitivity in the striatum and hyperexcitable D_2-containing neuron clusters:** Chronic antipsychotic use upregulates and sensitizes D_2 receptors in the basal ganglia. But these receptors do not function in isolation – D_2-containing neurons in the striatum become hyperresponsive to excitatory input, and increased 5-HT_{2A} receptor expression in the caudate-putamen further potentiates dopamine-mediated hypersensitivity. When the drug is withdrawn, excess dopamine stimulates these hypersensitive receptors, along with persistent glutamatergic overdrive and altered serotonergic modulation, leading to choreoathetoid movements, tremors, or akathisia
- **Reduced presynaptic dopamine autoreceptor inhibition and glutamate-driven excitation:** Normally, D_2 autoreceptors regulate dopamine synthesis and release. Chronic antipsychotic exposure dampens their function, and upon withdrawal, dopamine release increases uncontrollably, further exacerbating involuntary movements. At the same time, D_2-containing striatal hyperexcitability increases sensitivity to incoming glutamatergic transmission, while altered 5-HT_{2A} receptor function amplifies dopamine-dependent behavioral withdrawal
- **Disruption of glutamatergic, serotonergic, and cholinergic balance:** The basal ganglia rely on finely tuned glutamatergic, serotonergic, and cholinergic

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modulation of dopaminergic neurons. A sudden loss of D_2 receptor blockade alters these circuits, leading to an imbalance in excitatory and inhibitory transmission, contributing to excessive, dysregulated motor output. This glutamate-driven hypersensitivity in D_2-containing neurons is further shaped by serotonin receptor plasticity, as 5-HT_{2A} receptors exert an exaggerated modulatory influence on dopamine function in withdrawal states. Importantly, 5-HT_{2A} receptor blockade attenuates dopamine supersensitivity, suggesting that this might, in the future, represent a strategy for mitigating withdrawal effects

Histaminergic Resensitization

Many SGAs have H_1 histamine receptor antagonism, which contributes to sedation, weight gain, and appetite stimulation. Chronic blockade of H_1 receptors leads to adaptive receptor upregulation, as the brain compensates for the sustained inhibition of histaminergic neurotransmission.

Upon discontinuing an SGA with strong H_1 receptor occupancy, histaminergic neurons in the tuberomammillary nucleus become hyperactive, leading to rebound insomnia and heightened arousal. The degree of withdrawal symptoms relates to H_1 receptor occupancy. For example, at low doses (as little as 25 mg of quetiapine), up to 60–80% of H_1 receptors may be blocked. Therefore, histamine-related withdrawal effects may not manifest until the patient is tapered to lower doses, at which point histaminergic sensitivity is restored abruptly.

The loss of histamine blockade leads to increased nighttime awakenings, difficulty maintaining sleep, and heightened nocturnal arousals, making withdrawal-related insomnia particularly disruptive. This effect is more pronounced in patients who have relied on an SGA for sleep maintenance, as their intrinsic sleep–wake cycles become dysregulated.

A slow taper of SGAs with high H_1 affinity (such as olanzapine or quetiapine) allows for progressive receptor normalization, reducing withdrawal-related sleep disturbances.

5-HT_{2A} Receptor Rebound

SGAs also exert significant 5-HT_{2A} receptor antagonism, contributing to their sleep-promoting effects by enhancing deep, slow-wave sleep and decreasing nighttime awakenings. Chronic 5-HT_{2A} blockade increases receptor density and sensitivity, leading to accentuated serotonergic response upon discontinuation.

Withdrawal from SGAs results in decreased REM sleep, reduced total sleep duration, and diminished sleep efficiency, with these effects emerging within the first few days to weeks following discontinuation. The 5-HT_{2A} receptor system, which plays a crucial role in sleep maintenance, arousal inhibition, and sleep consolidation, undergoes a rebound effect when an antipsychotic is withdrawn, contributing to reduced sleep depth, increased awakenings, and heightened nocturnal arousal.

Further, the loss of 5-HT_{2A} antagonism leads to increased activation of wake-promoting circuits in the locus coeruleus and dorsal raphe nuclei (Vanover and Davis, 2010), disrupting the balance between serotonergic sleep regulation and noradrenergic arousal pathways. Patients who discontinue SGAs abruptly often experience vivid dreams, nightmares, and nocturnal anxiety, reflecting REM sleep fragmentation.

These withdrawal-induced sleep disturbances highlight the necessity of slow tapering, particularly in patients who have relied on antipsychotics for sleep regulation. A gradual dose reduction allows serotonergic and histaminergic systems to readjust, minimizing sleep disruption and improving post-withdrawal sleep quality.

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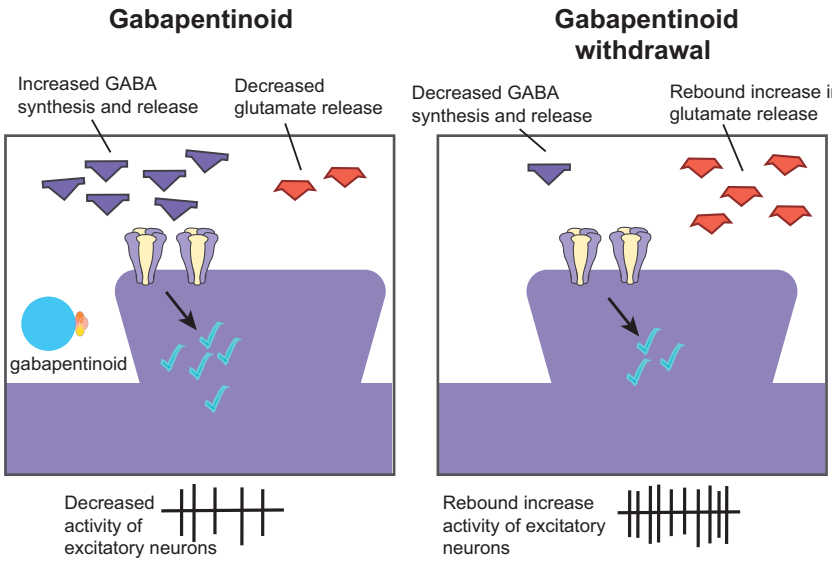


Figure 0.10 **Gabapentinoid withdrawal.** Gabapentin (and pregabalin) bind to the alpha-2-delta subunit of voltage-gated calcium channels (VGCCs), reducing calcium influx and excitatory neurotransmitter release (red polygons). This dampens synaptic transmission and increases inhibitory tone (blue check marks) that results from increased GABA (purple polygons) synthesis and release. Upon withdrawal (right), calcium channel activity rebounds, leading to increased excitatory neurotransmitter (glutamate) release and transient neuronal hyperexcitability. This may cause withdrawal symptoms like agitation, anxiety, and pain sensitivity until homeostasis is restored. The bottom trace shows increased neural firing after withdrawal, compared to suppression with gabapentin and pregabalin.

Gabapentinoids

Gabapentin and pregabalin exert their effects by binding to the alpha-2-delta subunit of voltage-gated calcium channels (VGCCs), reducing calcium influx and suppressing excitatory neurotransmitter release, particularly glutamate (Figure 0.10). Over time, neurons compensate by upregulating VGCC expression, increasing calcium channel density to maintain synaptic homeostasis.

When gabapentinoids are withdrawn, this compensatory upregulation increases calcium-dependent neurotransmitter release, causing a rebound increase in excitatory signaling. This may produce cortical excitability, manifesting as anxiety, agitation, restlessness, and, in severe cases, withdrawal seizures.

Additionally, gabapentinoid withdrawal may be associated with increased pain sensitivity (rebound hyperalgesia), autonomic instability, and insomnia, reflecting the loss of inhibitory neuromodulation. A slow taper allows VGCC expression to normalize gradually, preventing the abrupt surge in excitatory neurotransmission that characterizes gabapentinoid withdrawal.

Antihistamines

Histamine is a fundamental neuromodulator in the CNS and plays a critical role in wakefulness, arousal, cognition, and autonomic regulation (Brown et al., 2001). Originating from the tuberomammillary nucleus of the hypothalamus, histaminergic neu-

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rons project widely throughout the brain, exerting excitatory effects through H_1 and H_2 receptors while being tightly regulated by inhibitory H_3 autoreceptors (Brown et al., 2001). Given its pervasive influence on sleep–wake balance, attention, and homeostatic functions, histamine modulation is a common yet often overlooked mechanism of action for many psychotropic and general medical medications.

Antihistaminergic properties – whether intentional, as in sedating antihistamines, or incidental, as seen with certain TCAs, mirtazapine (Sato et al., 2013; Smith et al., 2007), and antipsychotics (e.g., quetiapine, olanzapine, clozapine) (Sato et al., 2015) – can significantly impact alertness, cognition, and sleep architecture (Yoshikawa et al., 2021). Understanding the consequences of histaminergic blockade, particularly in the context of medication discontinuation, is crucial for anticipating withdrawal effects, managing rebound symptoms, and optimizing treatment strategies for many medications, not just the "antihistamines."

Histaminergic neurons, located exclusively in the tuberomammillary nucleus of the hypothalamus, project throughout the brain, including into the hypothalamus, basal forebrain, and amygdala – regions integral to arousal regulation. However, unlike other aminergic neurons, histaminergic neurons lack somatodendritic autoreceptors; instead, H_3 receptors presynaptically inhibit voltage-dependent calcium channels, to modulate histamine release. Under stressful conditions (e.g., dehydration, hypoglycemia, external stressors), histamine release intensifies (Brown et al., 2001).

Chronic use of centrally acting antihistamines (e.g., diphenhydramine and hydroxyzine) downregulates H_1 receptors, decreasing their sensitivity to endogenous histamine. Upon discontinuation, the brain may compensate with an increase in histamine release, driven by the absence of H_1 blockade. Moreover, blocking H_1 receptors dampens excitatory signaling, suppresses wakefulness, produces sedation, and impairs alertness. However, with prolonged use, H_1 receptor expression is downregulated, and compensatory mechanisms emerge to counteract histamine suppression. When antihistamines are discontinued, histaminergic neurons, previously suppressed, reactivate with increased firing, leading to an excessive release of histamine. This increase now acts on a receptor system that is "primed" for increased sensitivity. The consequence: rebound wakefulness, increased nighttime arousal, and difficulty initiating sleep as well as potential anxiety. The histaminergic system, tightly linked to sleep–wake regulation, circadian rhythms, and homeostatic arousal mechanisms – including through orexin and other monoaminergic systems (Sakurai et al., 2021) – may amplify these effects.

Additionally, many antihistamines have anticholinergic properties, leading to muscarinic receptor downregulation. Upon discontinuation, there may be an increase in cholinergic activity, which produces dizziness, nausea, irritability, and, in some cases, rebound anxiety.

These withdrawal symptoms are particularly pronounced in long-term users, as histaminergic and cholinergic circuits take time to normalize.

The Deprescribing Journey Ahead

Deprescribing is not simply the reverse of prescribing. It is a deliberate, strategic process that requires just as much precision, clinical judgment, and understanding of pharmacology as initiating treatment. In the drug monographs ahead, we will provide a comprehensive roadmap for deprescribing psychiatric medications and addressing when, why, and how to discontinue them safely and effectively. Each psychotropic medication will be reviewed with a structured framework, ranking the challenges of

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deprescribing for each medication, and we will discuss key elements for safe deprescribing, including:

- **When and why to deprescribe (or consider deprescribing):** Medications should be discontinued when the risks outweigh the benefits, whether due to lack of efficacy, remission of symptoms, intolerable side effects, safety concerns, or patient preference. Some drugs should be prioritized for deprescribing based on their potential to cause harm if continued unnecessarily
- **Mechanisms and risks of withdrawal syndromes:** Discontinuation symptoms are not random. They emerge from predictable neurobiological mechanisms, including receptor upregulation, compensatory neurotransmitter changes, and homeostatic dysregulation. Some medications, such as high-potency benzodiazepines and short half-life SNRIs, pose particularly high risks for withdrawal due to their pharmacokinetics and pharmacodynamics
- **Medication-specific withdrawal symptoms – from partly cloudy to tornado:** Not all discontinuation syndromes are created equal. Withdrawal symptoms exist on a spectrum and by categorizing medications according to their withdrawal risk, we can tailor deprescribing strategies accordingly
- **Distinguishing withdrawal from relapse:** One of the greatest clinical challenges in deprescribing is determining whether a patient's emerging symptoms represent a true relapse of their underlying condition or merely transient withdrawal effects. We will provide strategies for differentiating withdrawal-induced anxiety, mood changes, and autonomic symptoms from actual disorder recurrence, helping clinicians make informed decisions about when to restart versus when to persist through the withdrawal period
- **Rapid versus slow discontinuation – when to taper and when to stop quickly:** Not all medications require slow tapering. Some can be stopped more abruptly under specific conditions. Others demand an ultra-slow, dose reduction to prevent withdrawal. We will explore evidence-based strategies for tapering, including when a moderate taper suffices and when a gradual reduction over months is necessary
- **Step-by-step tapering approaches:** Practical tapering schedules will be provided for each medication
- **Rating scales for monitoring discontinuation:** Symptom tracking helps distinguish withdrawal from relapse and guides tapering adjustments. We will review clinically useful rating scales for monitoring discontinuation-related symptoms
- **Risk factors for withdrawal symptoms:** Not all patients experience withdrawal the same way. We will discuss how factors like age, duration of use, underlying comorbidities, and cognitive variables (such as nocebo effects) shape an individual's withdrawal experience
- **Pharmacogenetics and drug metabolism in deprescribing:** A one-size-fits-all approach to tapering does not work. Genetic differences in cytochrome P450 metabolism (Bousman et al., 2023) and receptor sensitivity can dramatically influence withdrawal severity. We will explore how pharmacogenetics and other factors inform deprescribing (Strawn et al., 2023), explaining why some patients tolerate discontinuation well while others struggle with severe withdrawal effects
- **Cross-titration strategies for medication switching:** Deprescribing does not always mean stopping all treatment. Often, the goal is to transition from one medication to another with minimal disruption. We will cover cross-tapering

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techniques for switching between antidepressants, antipsychotics, mood stabilizers, and anxiolytics

 Tornado	Severe, and potentially problematic withdrawal. Symptoms can hit suddenly and escalate quickly, often requiring intensive management. Expect autonomic instability, severe mood swings, and possibly life-threatening symptoms if not appropriately tapered (e.g., benzodiazepines, high-dose venlafaxine)
 Severe Storm	Disruptive withdrawal with intense symptoms. Symptoms that are well recognized are often severe and can impair functioning, but careful tapering can help navigate the storm. Patients may experience dizziness, agitation, sensory disturbances, and mood instability (e.g., gabapentinoids)
 Gusty Winds	Withdrawal symptoms may be present in some patients or some situations and may be challenging to predict or unclear based on the evidence. These symptoms rarely turn into a full storm. Symptoms like restlessness, mild dizziness, or blood pressure fluctuations may occur (e.g., beta blockers, antipsychotics, most SSRIs)
 Partly Cloudy	Minor, fleeting symptoms that barely register. Maybe a little discomfort and the symptoms may or may not be even withdrawal related. When they're present, they pass quickly without significantly impacting daily function (e.g., antihistamines)

Deprescribing must be as intentional and precise as prescribing. A poorly planned discontinuation can lead to unnecessary distress, worsening symptoms, and loss of trust. However, a well-executed deprescribing strategy ensures a smooth transition off medication, reduces the risk of withdrawal and relapse, and, ideally, optimizes long-term outcomes.

Ultimately, psychopharmacology is not just about starting the right treatment – it's about knowing when and how to stop it. Just as the right medication at the right time can transform a patient's life, the right discontinuation strategy is similarly essential.

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