# Stahl's DEPRESCRIBER'S GUIDE

Deprescribing is not simply the reverse of prescribing – it is a strategic, patient-centered process that requires as much clinical judgment and pharmacological expertise as initiating treatment. Based on the principles of *Stahl's Essential Psychopharmacology Prescriber's Guide*, this new resource provides a structured, user-friendly manual for deprescribing psychotropic medications safely and effectively. Deprescribing includes both discontinuing medication altogether as well as discontinuing medication while starting another one (i.e., switching).

The medications are presented in a consistent format to facilitate rapid access to essential deprescribing information. Each drug monograph is divided into clearly delineated sections with distinct color backgrounds, allowing clinicians to quickly identify key details about when and why to deprescribe, the risks and mechanisms of withdrawal, tapering protocols, cross-titration strategies, and how to distinguish withdrawal symptoms from relapse. Deprescribing is complex since not all patients react to discontinuing a medication the same way, in fact showing vast differences from one patient to the next. We thus provide tips for those patients who have the most trouble when they try to stop a medication. Understanding that deprescribing a given medication is therefore certainly not the same for all, we nevertheless have categorized visually and whimsically all medications covered in this text by how much difficulty is associated with each, taking an overall point of view from clinical experience in deprescribing them. Thus, the ratings use a weather metaphor for predicting potential describing difficulties and range from the most difficult/problematic, called "tornado," to progressively less problematic, namely "severe storm," "gusty winds," and, finally, "partly cloudy." Just as for predicting the weather, these categories for the drugs included here can be variable for individual patients.

This guide is designed to be genuinely useful for clinicians by offering both evidence-based recommendations and expert clinical insights. The decision to deprescribe remains the responsibility of the clinician, and every effort has been made to provide accurate and up-to-date information in accordance with current standards of care. However, psychopharmacology is an evolving field, and neither the authors nor the publisher can guarantee that the information provided is entirely free of error, as clinical standards continue to change through research and regulatory updates. The authors and publisher disclaim any responsibility for the continued currency of this information and any liability for potential consequences arising from its use. Clinicians deprescribing these medications should remain vigilant and consult the latest guidance from regulatory agencies and manufacturers.

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"Psychiatric patients often receive several medications, some of which may no longer be needed, and which could be causing harmful side effects or adverse pharmacokinetic interactions. Thus, deprescribing is a critical and often necessary component of pharmacotherapy. This expertly written book by Drs. Strawn and Stahl contains comprehensive guidelines about the art of discontinuing, tapering, or switching psychotropic medications to improve patients' outcomes. It provides systematic details of the 'what, why, when, and how' of optimizing a psychotropic drug regimen via judicious deprescribing to avert or minimize the risks of polypharmacy in all age groups. Beautifully illustrated and generously referenced, the authors provide rating scales and checklists of the withdrawal symptoms of 64 widely used psychotropic medications, and differentiate them from relapse.

I believe this book is destined to become an indispensable, must-have reference for all psychopharmacology prescribers."
Professor Henry A. Nasrallah, MD, University of Cincinnati College of Medicine, Cincinnati, OH, USA

"While considerable research, multiple guidelines, and substantial clinical attention is paid to the question of which medication to prescribe, information and guidelines about when and how to discontinue medications scarcely get a mention. Until now. *Stahl's Deprescriber's Guide* authored by Drs. Jeffrey R. Strawn and Stephen M. Stahl provides the most authoritative guide on deprescribing psychotropic medications available. It covers 64 of the most widely used agents, managing the near impossible task of simultaneously being succinct and focused yet comprehensive and detailed. It is suffused with rare clinical wisdom answering the kinds of questions of greatest clinical relevance. It deserves pride of place on the bookshelf of every prescriber."

Michael Berk, MBBCh, MMed(Psych), FF(Psych)SA, PhD, FRANZCP, FAAHMS, FASSA Deakin Distinguished Professor of Psychiatry, School of Medicine, Deakin University and Barwon Health, Geelong, Victoria, Australia

"Deprescribing – the purposeful and monitored tapering and possible cessation of a medication deemed to be no longer relevant or appropriate within a treatment regimen – has become a critical focal point in the longitudinal management of numerous chronic or recurrent conditions throughout all areas of medicine. In psychiatry, its role has been largely misunderstood and relatively neglected until fairly recently. Drs. Strawn and Stahl provide readers with a well-annotated, scholarly, comprehensive overview of the logistics for deprescribing psychotropic agents, paying careful attention to the context, circumstances, implications, and practical implementation of deprescribing protocols across all major elements of the modern pharmacopoeia. Readers will be enlightened by their comprehensive yet practical drug-by-drug approach that includes pharmacokinetics, logistics for switching strategies, managing withdrawal phenomena and differentiating them from relapses, use of rating scales, and considerations for special populations. Clinicians at all levels of training and expertise will benefit from the wisdom imparted in this critical text."

Joseph F. Goldberg, MD
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President, American Society of Clinical Psychopharmacology
Deputy Editor-in-Chief, *The Journal of Clinical Psychiatry*

"Deprescribing medications is a necessary skill for all clinical psychopharmacologists, and is not a trivial task. Drs. Strawn and Stahl impart their collective wisdom as they meld their own experiences with what the medical literature informs us, giving us advice for implementing winning strategies. Sagely eliminating medications that interfere with others is essential to the practice of optimal, and personalized, care. The key concept is that while gradual dose reduction is often required to avoid 'rebound effects' there are other medications that can be safely stopped abruptly – the wise practitioner will know which ones are which. An example is the deprescribing of anticholinergic medications, a hot topic today, as this class of medications are often unnecessarily prescribed, and can lead to impairments in cognition as well as exacerbating tardive dyskinesia. Organized alphabetically, together with an index by drug class, the book is user friendly and thus easy to consult. Profusely illustrated with the award-winning figures that have made Stahl's series of books from Cambridge University Press famous, this book belongs on the shelves (and e-readers) of all clinicians involved in the care of people receiving psychotropic medications."

Leslie Citrome, MD, MPH
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"Deft pharmacological prescription of psychiatric medications in the treatment of mental disorders involves integrating results from efficacy and effectiveness studies with clinical experience. Initiating and optimizing pharmacological treatments has been the priority of clinical research and knowledge transfer to practising clinicians. Deprescribing psychiatric medication, however, has received relatively less consideration, resulting in a knowledge gap predisposing heterogeneity in practice, quality of care, risk of harm and cost-ineffectiveness of treatment. Drs. Jeffrey Strawn and Steven Stahl have provided a scholarly, timely, ready for primetime implementation guide to practitioners on the appropriate deprescribing of medications in psychiatry. Their guide is a thoughtful integration of the science and art recognizing the fundamentals of psychopharmacology yet considering aspects of safety, utility, and acceptability of treatments, filling the knowledge gap that is so critically and urgently needed."

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# CONTENTS

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This book would not have come together without the insight, patience, and talent of many collaborators and colleagues, each of whom made this *Deprescriber's Guide* stronger, clearer, and more clinically useful than we could have managed on our own. These individuals helped us conceptualize what this book is truly about: not just how to taper or stop a medication, but when to do so and why.

Too often, medications accumulate without regular reassessment. Benzodiazepines. Hypnotics. SSRIs. These treatments, once appropriate, can outlast their original purpose. But deprescribing isn't limited to these scenarios. It's a clinical habit that should be embedded in routine care, especially when patients are doing well. In a field with limited evidence and few formal guidelines, clinicians often rely on experience, intuition, and shared decision-making. This book offers practical strategies, clinical pearls, and insights we've gathered over decades – not as a textbook, but as a trusted colleague.

We are deeply grateful to Nancy Muntner, whose artistic vision and intuition transformed our ideas into figures that are clear, memorable, and alive. Nancy's illustrations don't just support the material – they teach it, helping our readers see what words alone cannot convey.

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Finally, we thank our patients, who have taught us more than any textbook, lecture, or randomized controlled trial ever could. They've shown us how deprescribing can be

liberating and when it can be destabilizing. They've helped us understand that stopping a medication isn't always a purely clinical decision; it's a profoundly personal one with roots in fear, hope, past experiences, the clinician–patient relationship, and identity. Most importantly, our patients have reminded us that deprescribing – like prescribing – is never the end of the conversation. It's the beginning of a new one.

Jeffrey Strawn and Stephen Stahl

# INTRODUCTION

## 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.

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.

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.

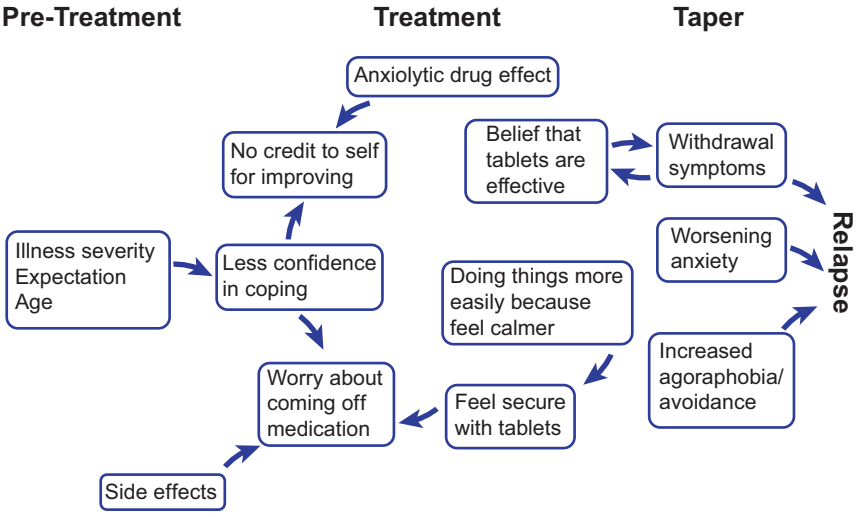


Figure 0.1 **Psychological factors affecting discontinuation of benzodiazepines.** Adapted from Başoğlu M, Marks IM, Kiliç C, Brewin CR, and Swinson RP. Alprazolam and exposure for panic disorder with agoraphobia: Attribution of improvement to medication predicts subsequent relapse. Br J Psychiatry 1994;164(5):652–659.

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).

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"*<br>Patients may believe their recovery is due to personal strength, not the medication, making them more likely to stop | *"Stopping meds means relapse"*<br>Many clinicians assume that stopping medication leads to worsening symptoms, making them hesitant to deprescribe<br>*"Last time a patient stopped, it didn't go well … "*<br>Past negative experiences stick in the clinician's mind | *If they stop, will everything fall apart?"*<br>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*<br>Many patients feel uneasy about needing medication long term<br>*Worry about withdrawal*<br>If they've had bad discontinuation symptoms before, they may expect them again – even if a slow taper could prevent them | *Fear of relapse*<br>Clinicians may overestimate the risks of stopping, leading them to continue medications out of caution rather than need<br>*Legal and ethical concerns*<br>Clinicians may fear blame if a patient relapses after stopping medication | *"What if stopping makes things worse?"*<br>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"*<br>Some patients see long-term medication as a failure<br>*"What if this is hurting me?"*<br>Concerns about side effects – real or feared – often drive patients to stop medication | *"If it's working, why change it?"*<br>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"*<br>Families may see the medication as the only thing keeping their loved one well – even when deprescribing is reasonable |

Table 0.1 (cont.)

| Factor | Patients | Clinicians | Family members |
|---|---|---|---|
| Expecting the worst (or the best) | *"If I stop, I'll have horrible withdrawal"*<br>Patients may experience withdrawal just because they expect it (nocebo effect)<br>*"If I stop, I'll be totally fine"*<br>Overconfidence can also be a problem, leading to abrupt stopping and relapse | *"This is going to end badly"*<br>Some clinicians expect tapering to fail before even trying<br>*"I have to protect the patient from themselves"*<br>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!"*<br>Some family members encourage stopping too soon<br>*"You're not well enough to stop"*<br>Others push to stay on meds indefinitely |
| Social pressures and influence | *Advice from the internet, social media, peers, therapists or other clinicians*<br>Patients may hear conflicting messages that shape their attitudes towards stopping<br>*Family pressure*<br>Sometimes loved ones push for stopping – or for continuing | *Guidelines vs. real-world experience*<br>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"*<br>Family input can be helpful – or make the process even harder |
| Avoidance and safety behaviors | *Fear of discomfort leads to avoiding tapering altogether*<br>Some patients never even try to stop because they're afraid of what might happen | *"Slow tapers are safer."*<br>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."*<br>Families may resist change if things are going well |

Table 0.1 (cont.)

| Factor | Patients | Clinicians | Family members |
|---|---|---|---|
| How past experiences shape beliefs | *If stopping went badly once, it must always go badly*<br>Patients with past withdrawal or relapse often develop a learned fear of tapering<br>*If stopping was easy once, it'll be easy again*<br>The opposite is also true – some people underestimate the risks based on a single experience | *Clinicians remember the disasters more than the successes*<br>A few bad experiences with stopping medication can make clinicians hesitant to deprescribe | *Family remembers the worst times*<br>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.

## 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 |

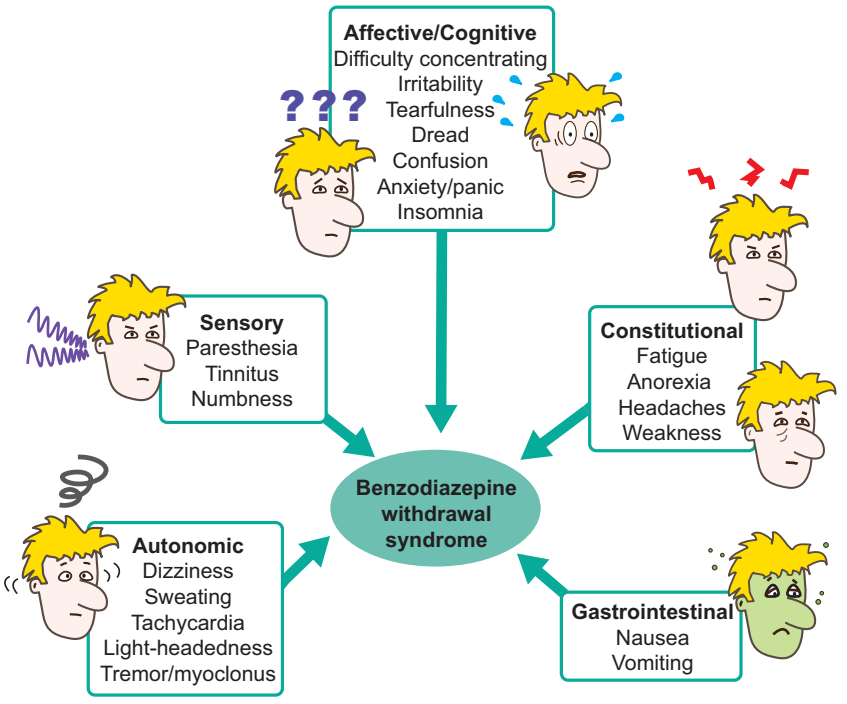


Figure 0.2 **Benzodiazepine withdrawal.** Benzodiazepine withdrawal often represents a full-body rebound of hyperexcitability, affecting multiple systems. Withdrawal is not just a reversal of benzodiazepine effects – it's a neurobiological rebound that can be severe, prolonged, and distressing.

### *$GABA_A$ 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).

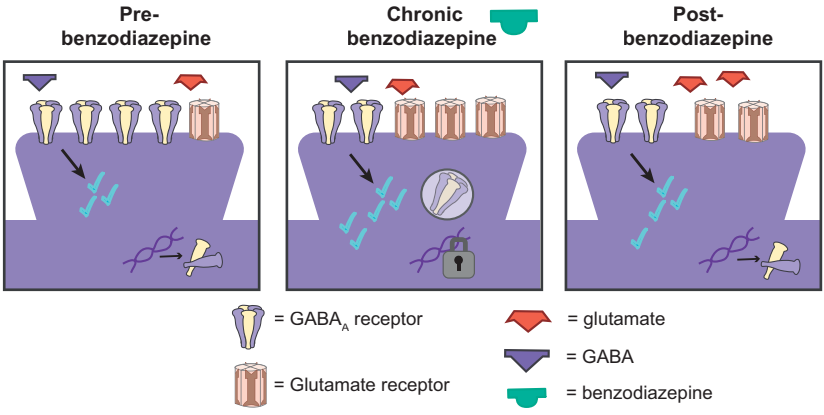


Figure 0.3 **Neurobiology of chronic benzodiazepine treatment and withdrawal.** Following administration of a benzodiazepine, GABA$_A$ receptors (purple and cream) are downregulated and glutamate receptors (brown and tan) are upregulated. The GABA$_A$ receptors later become less sensitive because of 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.

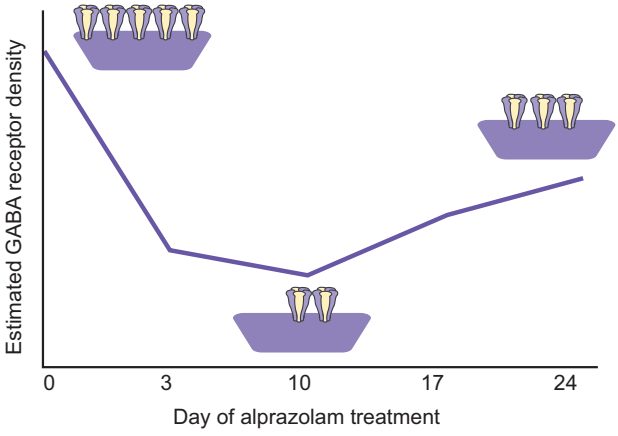


Figure 0.4 **Changes in GABA$_A$ receptor density during benzodiazepine treatment.** Changes of benzodiazepine receptors during chronic benzodiazepine administration in humans. Adapted from Fujita M, Woods SW, Verhoeff NPLG, et al. Changes of benzodiazepine receptors during chronic benzodiazepine administration 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.

### *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.

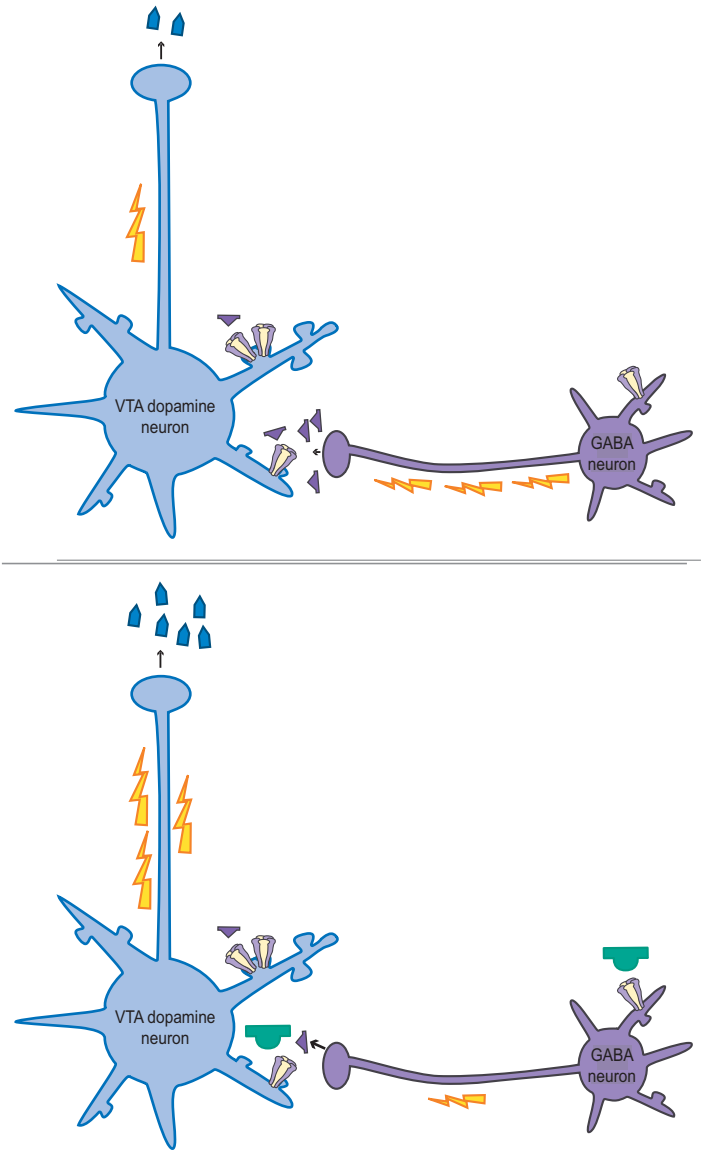


Figure 0.5 **GABA regulates dopamine release in the ventral tegmental area (VTA).** The activity of dopaminergic neurons (blue) in the VTA is influenced by tonic GABAergic tone (purple neuron). In the bottom panel, benzodiazepine administration (green polygon) increases the inhibitory effect on these 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.

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.

### 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.

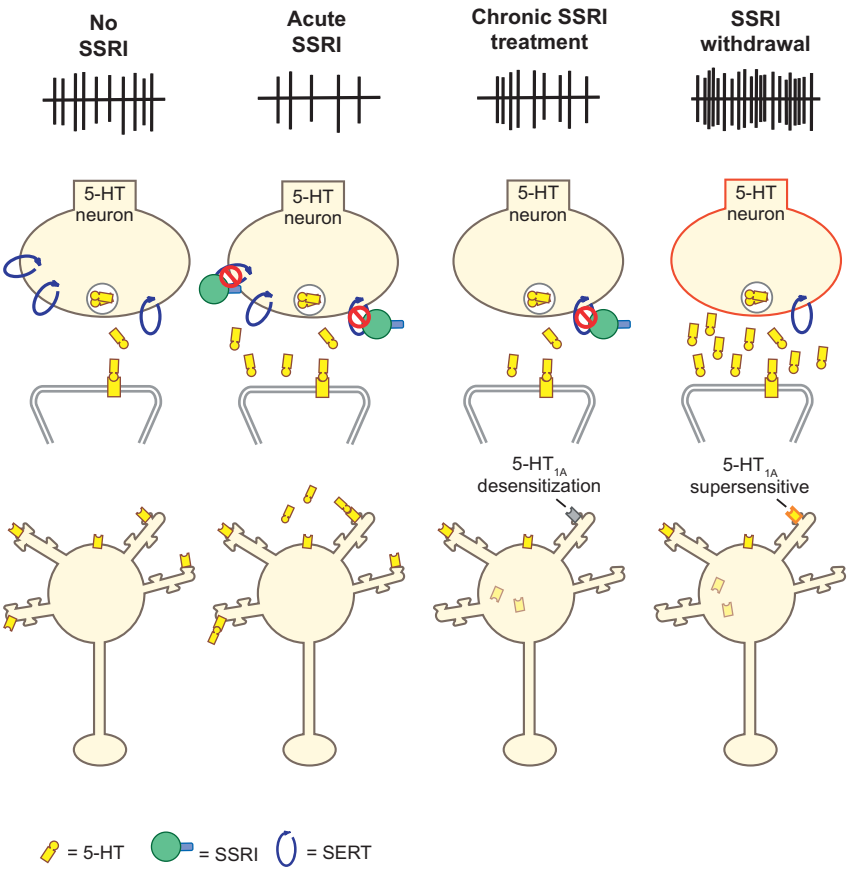


Figure 0.6 **Selective serotonin reuptake inhibitor (SSRI) initiation and withdrawal.** SSRIs initially reduce serotonergic neuron firing due to increased activation of 5-$HT_{1A}$ autoreceptors, which undergo internalization over time. Concurrently, serotonin transporter (SERT) inhibition increases 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.,