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Challenges And Strategies in Antidepressant Discontinuation for Major Depressive Disorder and Anxiety Disorders: Rationale, Review of Tapering Protocols and Psychological Interventions

Shreyas Shrikant Pendharkar[1], Preeti Sadhu Pendharkar[2], Apoorv Shah[3], Bhupinder Singh[4]

[1]Associate Professor, Department of Psychiatry Chirayu Medical College & Hospital Bhopal, 0000-0003-3578-7846
[2]Lecturer & PhD, scholar department of Psychology Barkatullah University Bhopal, 0009-0004-3523-7742
[3]Senior Resident, Department of Psychiatry Chirayu Medical College Hospital Bhopal, 0009-0008-2454-325X
[4]Prof & Head, department of Psychology Barkatullah University Bhopal, 0009-0003-6218-903X

Corresponding Author:

Apoorv Shah
Senior Resident Department of Psychiatry Chirayu Medical College Hospital Bhopal,
drapoorvshah@gmail.com

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ABSTRACT

Major Depressive Disorder (MDD) and anxiety disorders along with obsessive-compulsive disorder (OCD), and Post-Traumatic Stress Disorder (PTSD), pose significant global health burdens, affecting over 280 million of people globally. Standard care for MDD and anxiety disorders including OCD and PTSD involves antidepressants (AD), Cognitive Behavioral Therapy (CBT), or both in conjunction, tailored to individual patient's symptom severity. Post-remission, all major treatment guidelines recommend gradual AD tapering with relapse prevention interventions, but antidepressant (AD) discontinuation is complex due to withdrawal symptoms mimicking relapse, physiological dependence from prolonged use, and patient-specific factors like mental health history and treatment duration, further complicated by frequent comorbidity of major depressive disorders and anxiety disorders including OCD& PTSD. Traditional guidelines generally advocate antidepressant (AD) tapering to proceed in fixed schedule linear tapering over few weeks to months, but lack detailed step by step hands on approach or identifying & mitigating antidepressant (AD) withdrawal symptoms; leading to misdiagnosis, prolonged AD use, and reliance on unverified online cessation advice. Updated NICE and Royal college of Psychiatrists guidelines now endorse hyperbolic or proportional tapering, individualized to patient needs, supported by CBT and Mindfulness-Based Cognitive Therapy (MBCT) to mitigate withdrawal, enhance emotional regulation, and reduce relapse risk across these disorders. Effective deprescribing requires meticulous planning, patient education, and monitoring to integrate these evidence-based strategies, curbing unnecessary AD use amid rising global reliance. Gaps in prescriber awareness highlight the need for research into neurobiological mechanism of physical dependence due to antidepressants (AD) and adaptable dosing formulations to refine AD tapering protocols and improve outcomes in MDD and anxiety disorders including OCD & PTSD management.

Keywords*: Antidepressants, Deprescribing, Major Depressive Disorder, Anxiety Disorders, Proportionate taper, Psychotherapy, Lifestyle interventions.*

INTRODUCTION

Major Depressive Disorder (MDD) is a significant global health challenge, ranked as the third leading cause of disease burden by the World Health Organization in 2008 [1] and 30th in Disability-Adjusted Life Years (DALYs) in 2019, with a 52.1% increase in DALYs since 1990 [2]. In 2019, approximately 246 million people worldwide were affected, with females showing a 1.8:1 prevalence ratio over males [2]. Anxiety disorders, including Generalized Anxiety Disorder

(GAD), obsessive-compulsive disorder (OCD), and Post-Traumatic Stress Disorder (PTSD), also contribute heavily to global morbidity. GAD affects 301 million people, OCD 24 million, and PTSD 87 million, with DALY increases of 45–55% since 1990 [2]. These conditions often co-occur with MDD, and may need longer duration treatment.

Antidepressants (ADs) are a cornerstone of treatment for MDD and anxiety disorders, and their long-term use has surged. Between 2000 and 2023, AD prescriptions without psychotherapy rose globally, with 12.7–16.8% of populations in high-income countries using ADs continuously [3]. In OCD, 60–80% of patients receive SSRIs long-term [4], while 50–70% of PTSD patients receive multiple antidepressants (AD) simultaneously [5]. For MDD, 30–50% of long-term antidepressant (AD) prescriptions persist without evidence-based justification [6], driven more by relapse fears rather than legitimate need. This trend, coupled with side effects (e.g., sexual dysfunction) and patient preferences, underscores the urgency of safe AD deprescribing strategies [7, 8]. The Maudsley Deprescribing Guidelines released in 2024 offer structured tapering protocols for ADs, benzodiazepines, and gabapentinoids, emphasizing gradual reduction [9].

Current major treatment guidelines, such as those from the American Psychiatric Association (APA 2010), advocate gradual AD tapering post-remission but lack step by step hands on details on managing antidepressant (AD) withdrawal symptoms, which can affect up to 56% of patients on long term AD treatment (e.g., "brain zaps," malaise, anxiety symptoms) and are often misdiagnosed as relapse [10]. Antidepressant (AD) withdrawal symptoms can mimic relapse across disorders [11]. Effective discontinuation requires patient education, careful planning, and adjunctive interventions. This review aims to highlight the existing lacunae in major treatment guidelines for MDD and various anxiety disorders including OCD & PTSD. It also aims to collate evidence on proportional or hyperbolic antidepressant (AD) tapering protocols along with role of psychological interventions—Cognitive Behavioral Therapy (CBT), Mindfulness-Based Cognitive Therapy (MBCT), lifestyle modifications to support AD tapering and cessation in MDD, GAD, OCD, and PTSD.

Current Treatment Guidelines for Antidepressant (AD) Use in Major Depressive Disorder (MDD) And Their Potential Limitations

Current guidelines for Major Depressive Disorder (MDD) treatment advocate a phased approach involving Antidepressant (AD) medications and Cognitive Behavior Therapy (CBT) [10,12-13]. The acute phase (6-12 weeks) targets symptom remission with 12-16 CBT sessions (45-60 minutes each) focusing on challenging negative thoughts, enhancing coping skills, problem-solving, and self-esteem. The continuation phase (6-12 months) involves less frequent CBT (every 2-4 weeks) to reinforce skills and prevent relapse, while the maintenance phase (>12 months or indefinite) for high-risk patients uses CBT every 2-3 months to sustain gains, with recovery defined as 6 months of remission. Treatment duration should be individualized to reduce relapse risk. However, all major Current guidelines for prescribing antidepressants (ADs) in Major Depressive Disorder (MDD) largely depend on a key study—a meta-analysis—that found a 70% lower risk of relapse when patients continued AD treatment [14]. However, this study has flaws. For example, it involved quickly reducing AD doses (rapid tapering) and only tracked patients for a short time, which might mean some symptoms mistaken for a relapse were withdrawal effects from abruptly tapering &stopping the antidepressant (AD) medication [15]. Newer research adds to the doubt, showing that relapse rates may not differ much whether patients stay on ADs for a short or long time, challenging the idea of sticking to traditional treatment phases [16]. There is also a lack of long-term randomized controlled trials (RCTs) to provide stronger evidence. On top of that, the STAR*D trial, a real-world landmark study, found that, after achieving remission, continuing ADs for 12 months only reduced relapse rates by 16%, and even this result might be skewed because withdrawal symptoms could have been mislabeled as relapse [17].

Current Treatment Guidelines for Antidepressant (AD) Use in Anxiety Disorders, OCD, and PTSD And Their Potential Limitations

Current guidelines endorse cognitive-behavioral therapy (CBT) and antidepressant (AD) medication as primary treatments for anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) [18]. CBT includes cognitive restructuring, exposure therapy (e.g., exposure and response prevention for OCD, trauma-focused CBT for PTSD), skills training, and mindfulness and is deemed Equi-efficacious to Antidepressant (AD) medications [19]. Combination therapy (CBT + AD) is advised for severe cases or poor response, with CBT or ADs recommended for up to 2 years to prevent relapse [19, 20]. Remission is defined as near-complete symptom relief for ≥3 months [20]. Discontinuation of antidepressant (AD) medications triples relapse risk (risk ratio = 3.11, based on 28 RCTs, N = 4,995) [21], but this evidence is weakened by following factors. Majority studies are pharmaceutical industry funded, each study has its own criteria to define relapse, every study has used its own arbitrary AD tapering methods, and each study also has variable follow-up periods. There is considerable overlap between antidepressant (AD) withdrawal and relapse of underlying condition (anxiety symptoms) which is a significant limitation.

Reassessing Antidepressant (AD) Efficacy and role of Psychotherapy in Relapse Prevention for MDD and various Anxiety disorders, OCD & PTSD

A Cochrane Review by Machmutow et al. (2019) evaluated relapse prevention in persistent depressive disorder across 840 participants, finding that relapse rates were similar (13%) whether patients continued antidepressant (AD) treatment

for 6 months or extended it beyond that duration, compared to a notably higher relapse rate of 34% in those receiving placebo [22]. This suggests ADs offer a modest protective effect, quantified by a Risk Ratio (RR) ranging from 1.3 to 1.4, indicating a slight reduction in relapse likelihood compared to placebo. Importantly, the review also found that ongoing psychotherapy—specifically cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT)—performed as effectively as ADs in preventing relapse, highlighting their comparable efficacy. These findings were reinforced by the ANTLER trial (2021), which investigated patients with a history of major depressive disorder (MDD) who stopped AD treatment after long-term use. The trial revealed that more than 50% of these individuals remained well and free of relapse for up to 2 years after antidepressant (AD) discontinuation. [23] Another Cochrane review (Van Leeuwen et al., 2021) of 35 RCTs (N = 4,995) found elevated relapse risk with abrupt (Hazard Ratio [HR] = 2.09) as well as gradual (short linear antidepressant (AD) taper less than 4 weeks duration) antidepressant discontinuation (Hazard Ratio [HR] = 2.97), but combining psychological interventions (e.g., Preventive Cognitive Therapy, MBCT) with similar tapering schedule yielded 40%-75% success rates (Hazard Ratio [HR] = 0.89) [24]. Evidence quality was considered as low due to limited RCTs, very short antidepressant (AD) tapering durations, and small samples across the studies.

Presently, all major treatment Guidelines recommend gradual AD tapering over weeks to months but do not spell out specific step by step approach [10,12-13], with NICE guidelines since 2022, shifting to proportional or hyperbolic tapering approach over their earlier 2019 recommendation of 4-6 weeks linear dose reduction to taper and stop antidepressants (AD). CANMAT (2023) guidelines talk about a 'pragmatic approach' in tapering AD, but do Not offer any detailed step by step AD tapering guide to help to treating physicians [13,12]. A review of 21 major clinical guidelines showed that all guidelines advocated antidepressant (AD) tapering over 4-week to 6-month duration but lacked standardized step by step tapering protocols. Guidelines also did not offer any specific details about exact role of psychotherapeutic interventions (e.g., CBT, IPT frequency) during the antidepressant (AD) tapering process, and most importantly, no guidelines differentiated between (AD) withdrawal symptoms from relapse of underlying condition (Major Depressive Disorder (MDD) or anxiety disorders) [25].

Real-World Barriers to Antidepressant (AD) Tapering: Beyond the Guidelines

Eveleigh et al.'s 2017 RCT [26] investigated antidepressant (AD) discontinuation in 146 primary care patients on long-term (≥9 months) therapy without clear need. The intervention group (n=70) underwent guideline-based tapering, while controls (n=76) continued usual care. Non-compliance was high (49%) in the intervention group, with only 6% patients managed to stop antidepressant (AD) medications vs. 8% in controls. Relapse rates were unexpectedly higher in the intervention group (26%) than controls (13%), suggesting tapering guidelines may overestimate their practicality and underestimate AD withdrawal symptoms risks. Factors such as limited patient readiness, discontinuation symptoms, fears of relapse, and reliance on ADs—termed "legacy prescribing"[7]. —alongside physician barriers (e.g., time constraints, vague guidance) and caregiver concerns, perpetuate prolonged use.

Long-Term Antidepressant (AD) Use: Adverse effects, Emotional Blunting, and Physical Dependence challenges

Long-term antidepressant (AD) use poses risks including increased risk of gastrointestinal bleeding, sleep disturbances, sexual dysfunction, emotional blunting, weight gain, and increased risk of type 2 diabetes risk with cohort studies also linking it to higher rates of hyponatremia, fractures, and falls (Coupland et al., 2018) (27), and elevated cardiovascular disease and mortality risks after 5years continued use associated with all classes of antidepressants (AD), including the most commonly prescribed selective serotonin reuptake inhibitors (SSRI) for which the risk of cardiovascular events related mortality increased at 10 year mark (Bansal et al., 2022) (28). Emotional blunting, a debated side effect vs therapeutic effect phenomenon describes dulls emotions, both positive as well as negative (all spheres of emotions) beyond anhedonia, which is a core feature of MDD. It is unrelated to treatment duration (Goodwin et al., 2017) (29), It is measurable by the Oxford Depression Questionnaire (Christensen et al., 2021) (30), and tied to reduced feedback sensitivity, which is supposedly responsible for anti-obsessional properties of SSRI class antidepressants (Langley et al., 2023) (31).

Physical dependence on antidepressants (ADs) was recognized as early as 1959, with 18% of imipramine users reporting withdrawal symptoms like restlessness and insomnia (Mann & MacPherson, 1959; Andersen & Kristiansen, 1959) (32-33). Another example is 'Antidepressant (AD)-withdrawal mania,' a rare but severe syndrome characterized by irritability, aggression, and psychosis, emerging within a week of abrupt AD discontinuation. A case series of 32 patients documented this phenomenon, noting that it responded poorly to antipsychotics and mood stabilizers, often necessitating the re-administration of the original antidepressant to resolve symptoms (Andrade, 2004) (34).

Distinguishing Physical Dependence due to prolonged Antidepressant (AD) Use from Addiction

Antidepressants (ADs) can induce physical dependence, marked by tolerance and withdrawal symptoms. This is a normal physiological adaptation to prolonged use, not addiction, as ADs lack the euphoric, reinforcing properties tied to compulsive use and craving occurring due to a substance of abuse (9,11,35). Physical dependence only reflects human body's homeostatic adjustments, with withdrawal risks varying by AD class and their respective half-lives, while addiction as a phenomenon involves euphoria and impaired control. The DSM-5 clarifies that tolerance and withdrawal are expected with CNS drugs, not addiction indicators (36).

Antidepressant (AD) Withdrawal Syndrome: Terminology, Mechanisms, and Clinical Features

Antidepressant (AD) withdrawal syndrome, affecting over 56% of patients, emerges within 36–92 hours of abrupt cessation or rapid linear tapering of AD and is particularly very severe with short half-life drugs (e.g., paroxetine, venlafaxine) and relatively mild with slightly later (up to 1 week of stopping) onset, with long half-life drugs like fluoxetine. Antidepressant (AD) withdrawal symptoms can occur even after only 4–8 weeks of continued use and is also seen in healthy volunteers receiving (38-42). Withdrawal symptoms such as fatigue, malaise, "brain zaps," and irritability can persist for months and it is reported with all class antidepressants, causing significant distress. The term "withdrawal symptoms" is now favored over "discontinuation syndrome" by the Royal College of Psychiatrists and NICE guidelines, reflecting their acknowledgement of antidepressant (AD) induced physical dependence. This is a shift from industry-driven terminology 'Antidepressant (AD) discontinuation syndrome' which came into force because of benzodiazepine like addiction concerns (13,37-40, 45). PET studies link withdrawal to prolonged 5-HT1A receptor downregulation (8–60 months post-cessation), a neuroadaptive mismatch after serotonin transporter (SERT) blockade cessation (43-44). Over 43 symptoms are described spanning physical, neurological, mood, and cognitive domains, mimicking relapse but distinguished by novel physical symptoms like 'brain zaps, vertigo, akathisia or restlessness, hyperarousal' etc. which rapidly reverse within 12–48 hours upon AD re-administration in contrast to expected response time of relapse/recurrence of underlying pathology (MDD or anxiety disorders), where up to 2 weeks are expected for therapeutic effects (40-42).

Reported Antidepressant (AD) Withdrawal Symptoms (40-42)

- **Physical**: Nausea, abdominal cramps, flu-like symptoms, lethargy, fatigue
- **Neurological**: "Brain zaps," blurred vision, tingling, vertigo, hyperarousal
- **Sleep**: Insomnia, vivid dreams, nightmares
- **Mood**: emotional lability, agitation, crying spells, panic attacks
- **Cognitive**: Headache, Confusion, memory issues& poor concentration
- **Other**: hallucinations, akathisia, dysphoria to frank manialike symptoms (rare)

Role of Psychological Interventions and Lifestyle modifications For Successful Antidepressant (AD) Discontinuation and Relapse Prevention

Research over last decade shows that, cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy (MBCT), paired with lifestyle interventions like exercise and diet, can help patients taper off long duration antidepressants (AD) safely.

Cognitive Behavioral Therapy (CBT): A 2023 study found that internet-based CBT (iCBT) reduces symptoms during AD tapering with a moderate effect size of 0.54 [46]. In 2018, researchers tested CBT during antidepressant (AD) tapering in a controlled trial and found that, CBT components like cognitive restructuring and problem-solving—help patients cope with AD withdrawal symptoms like brain zaps, anxiety; though severe baseline depressive symptoms and poor treatment adherence were predictors of worse outcomes [47]. Another 2021 study compared CBT plus tapering versus continuing with antidepressants (AD) in 289 patients; after two years, relapse rates were nearly identical—27% versus 29%—showing CBT can hold its own and CBT has a protective role [48]. Severe baseline depressive symptoms & poor treatment compliance can weaken the impact of CBT [47].

Mindfulness-Based Cognitive Therapy (MBCT): MBCT mixes mindfulness techniques staying present and calm with CBT to tackle rumination and emotional dysregulation. A 2010 trial showed MBCT reduced relapse rates by 34% in people with recurrent depression as they attempted AD taper [49]. In 2016,PREVENT trial, a study with 424 patients, where MBCT with Antidepressant (AD) tapering support versus staying on AD was compared; relapse rates were similar, 44% versus 47% after two years—but the MBCT group reported better quality of life, and subjectively better coping andmindfulness practices group was found to have to lower symptom severity [50].Williams et al. (2024) conducted a pilot randomized trial with 40 adults tapering antidepressants (AD) testing brief Mindfulness-Based Cognitive Therapy (MBCT) (51).Patients were split into 20 each with intervention group received 4weekly MBCT plus AD tapering& 20 in control group received decided upon AD tapering only without any interventions.MBCT group had reduced symptom severity based on validated scales compared to control group's higher symptom persistence. Mindfulness practice correlated with enhanced emotional regulation during difficult withdrawal symptoms phase. This small study suggests brief MBCT may aid tapering, pending larger more structured trials.MBCT's metacognitive awareness helps patients tolerate antidepressant (AD) withdrawal symptoms like, brain zaps, anxiety symptoms, irritability and has moderate efficacy with effect size 0.48 across the studies, though its usually adopted 8-week format may be a challenge for treatment adherence [50-51,54].

Lifestyle interventions: Schuch et al. (2023) combined a meta-analysis and RCT on exercise as a treatment modality for major depressive disorder (MDD) The meta-analysis of 25 studies, adjusted for bias, confirmed exercise reduces depressive symptoms broadly. Separately, an RCT tested 60 adults tapering antidepressants (AD): 30 did a 12-week exercise program, 30 tapered AD as per treating physicians' advice only. The exercise group in the RCT had greater symptom improvement than the tapering-only control. Exercise showed benefits for mood and health in both analyses

with exercise as intervention effect size of 0.62 rivalling antidepressant (AD) efficacy [52]. In 2017, SMILES trial found that, Mediterranean diet (fish, green leafy vegetables, olive oil etc.) lowered depressive symptoms, with moderate effect size of 0.72 making AD tapering smoother through its anti-inflammatory effects [53]. These interventions cannot replace Antidepressant (AD)treatment but, Exercise is shown to enhance hippocampal volume and Brain-Derived Neurotrophic Factor (BDNF) levels, thus adding a natural layer of support due to their effects on neuroplasticity [55].

Patient-Centered Strategies for Effective Antidepressant Tapering

Effective discontinuation of antidepressants (ADs) requires a gradual, patient-specific tapering regimen to mitigate withdrawal symptoms, as abrupt cessation or rapid linear dose reductions heighten such risks [9,13, 45]. Evidence supports a proportional or hyperbolic tapering approach, characterized by progressively smaller dose reductions as the total dosage decreases, with systematic monitoring for withdrawal symptoms following each adjustment [9]. Subsequent reductions should be contingent upon the patient's symptomatic response, proceeding iteratively until the target dose or complete cessation is achieved. Tapering to minimal doses prior to discontinuation ensures that the final reduction is consistent with previously tolerated steps, thereby reducing both the incidence and severity of withdrawal through this symptom-guided methodology.

Table 1: Proportional or Hyperbolic Taper Strategy: Generic Example (9,13,45)

Week	Dose (mg/day)	Reduction (%)	Notes
1-4	15	25%	Initial reduction
5-10	11.25	25%	Reduction from 15mg
11-16	9	20%	Gradual reduction
17-22	7.2	20%	Continued gradual reduction
23-28	5.6	22%	Further reduction
29-34	4.2	25%	Larger reduction before final taper
35-40	2.1	50%	Final taper before discontinuation
41	0	100%	Discontinuation

Note: This table illustrates a hypothetical example (drug X) of proportional tapering and will require adjustments based on individual patient drug class and their needs.

Evidence for efficacy of Proportionate or Hyperbolic Tapering strategy for Antidepressants (AD)

Van Os J and Groot PC (2023) studied 3,956 patients in the Netherlands (2016-2021), finding a 75% success rate with hyperbolic tapering over 1-3 years, with mild to moderate AD withdrawal symptoms, mean Discriminatory Antidepressant Withdrawal Symptoms Scale (DESS) (41) score of 12.7 (56). Lower success was linked to longer duration of prescription antidepressant (AD) use, higher AD doses, female gender, younger age of onset of illness, and paroxetine/venlafaxine use; daily dose reductions by specifically designed tailor made 'tapering strips' outperformed weekly ones.

Royal college of Psychiatrists and NICE guidelines (2022) also (13, 45) endorse proportional tapering (10-25% of prior dose) or a 50% reduction to minimal effective dose followed by gradual descent for antidepressants, benzodiazepines, and Z-drugs. This minimizes withdrawal by reducing doses proportionally. However, alternate-day or third-day dosing fails for most antidepressants (half-lives <24 hours), causing withdrawal from fluctuating levels, except for fluoxetine (half-life 7-15 days), which tolerates less frequent dosing (9). Proportionate or Hyperbolic tapering with step-by-step withdrawal symptoms guided approach is thus favored for safer discontinuation than fixed dose linear tapering of antidepressant (AD) medications.

CONCLUSIONS

Delayed recognition of antidepressant (AD) withdrawal severity within healthcare systems has historically contributed to misdiagnosis, prolonged AD use, and patient reliance on unqualified sources for discontinuation guidance. Contemporary guidelines from authoritative bodies, such as the National Institute for Health and Care Excellence (NICE) and the Royal College of Psychiatrists, now advocate hyperbolic or proportional tapering strategies, tailored to individual patient needs, to mitigate withdrawal symptoms effectively. Integration of psychological interventions, including Cognitive Behavioral Therapy (CBT), Mindfulness-Based Cognitive Therapy (MBCT), and lifestyle interventions can enhance coping mechanisms and further reduces withdrawal impact. Despite these advances, challenges persist, notably inadequate prescriber education, which underscore the need for updated training, revised guidelines, and innovative dosing solutions. Ongoing research is essential to refine tapering protocols, elucidate AD dependence mechanisms, and curb long-term legacy prescribing, ultimately minimizing medical harm from unrecognized withdrawal.

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