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Withdrawal Syndrome Associated with Antidepressant Discontinuation: A Comprehensive Review of Symptoms, Risk Factors, and Management Strategies

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ABSTRACT

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are prevalent mental health conditions often treated with antidepressants, including SSRIs, SNRIs, tricyclic antidepressants, and benzodiazepines. However, abrupt discontinuation or rapid dose reduction of these medications can lead to withdrawal syndromes, ranging from somatic symptoms like dizziness and nausea to psychological effects such as mood swings and suicidal thoughts. This study examines withdrawal events associated with various antidepressants, emphasizing the need for effective health management strategies. The research aims to review withdrawal symptoms across antidepressant classes, identify high-risk medications, and explore alternative tapering methods such as hyperbolic dose reduction. A systematic literature review analyzed clinical studies, case reports, and patient surveys to evaluate withdrawal prevalence, symptom severity, and duration. Findings indicate that short half-life antidepressants (e.g., paroxetine, venlafaxine) pose elevated withdrawal risks, with symptoms persisting from weeks to years. Hyperbolic tapering demonstrated reduced severity in cases like escitalopram withdrawal. Persistent post-withdrawal disorders, including post-SSRI sexual dysfunction (PSSD), were documented. The research underscores the importance of structured discontinuation protocols and clinician awareness in mitigating withdrawal effects within healthcare systems. Implications highlight the necessity for evidence-based clinical guidelines on antidepressant tapering and enhanced patient education initiatives to prevent non-compliance and abrupt cessation. Future research should investigate long-term outcomes of withdrawal management strategies in diverse care settings.

KEYWORDS *antidepressant, withdrawal symptoms, SSRI, SNRI, tapering strategies.*

INTRODUCTION

Mental disorders are characterized by significant clinical disturbances in each individual such as consciousness, emotional development, or habits. Many types of mental disorders, such as bipolar, post-traumatic stress disorder, schizophrenia, eat disorder, anxiety disorder, and depression (Organization, 2022). In 2019, 280 million people suffer from depression, including 23 million children and adults (Kumbet et al., 2023).

Depression is a difference from the usual fluctuations in feelings and emotional responses that change every day. During a period of depression, a person feels sad, irritable, and feels empty, or loses interest in activities, almost every day for at least two weeks (Kumbet et al., 2023). The depression spectrum includes depressive and bipolar disorders, one of the symptoms included in depression is major depressive disorder (MDD) (Del Barrio, 2017).

In 2019, 301 million people suffer from anxiety disorder including 58 million children and adults. Characteristics from anxiety disorder are excessive fear, worry, and habit disorders (Kumbet et al., 2023). The anxiety spectrum includes anxiety disorders, obsessive-compulsive disorders, and traumatic stressor disorders. One of the symptoms included in anxiety disorders is generalized anxiety disorder (GAD) (Del Barrio, 2017).

Depression and anxiety disorders cause suffering that is very dangerous for physical and mental health, so effective therapeutic strategies are needed, for example the use of

antidepressants (Cosci et al., 2015). Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, benzodiazepines, quetiapine, and atypical antidepressants are effective antidepressants and are widely used in primary care (Foreman et al., 2020).

In addition, long-term antidepressant treatment makes users non-compliant and abruptly discontinued (Fava et al., 2015). Abrupt cessation or gradual reduction may cause a withdrawal reaction. Withdrawal syndrome is the emergence of a predictable constellation of signs and symptoms after abrupt cessation or rapid reduction of a psychoactive dose (Lerner & Klein, 2019).

RESEARCH METHOD

This study employs a systematic literature review as the primary research method to comprehensively analyze withdrawal syndromes associated with antidepressant discontinuation. The research focuses on peer-reviewed journal articles, clinical studies, case reports, and patient surveys published between 2010 and 2023. The data population consists of all available studies addressing antidepressant withdrawal symptoms, risk factors, and management strategies. A purposive sampling technique is used to select relevant studies based on predefined inclusion criteria, such as focus on SSRIs, SNRIs, tricyclic antidepressants, and benzodiazepines, as well as withdrawal symptom documentation. The final data sample includes 50 high-impact studies identified through databases like PubMed, ScienceDirect, and Cochrane Library.

The research instrument involves a structured data extraction form to systematically collect information on study design, sample characteristics, withdrawal symptoms, and tapering methods. To ensure validity, the selected studies are evaluated using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist, while reliability is maintained through dual independent screening by two researchers to minimize bias. Data collection techniques include database searches using keywords such as "antidepressant withdrawal," "discontinuation syndrome," and "tapering strategies," followed by manual screening of references to identify additional sources. The procedure involves three phases: (1) identification of studies, (2) screening based on relevance, and (3) final selection for in-depth analysis.

For data analysis, qualitative thematic analysis is conducted to categorize withdrawal symptoms, risk factors, and management approaches. Quantitative data, such as prevalence rates and symptom duration, are analyzed using descriptive statistics. NVivo software is utilized to organize and code qualitative data, while SPSS is employed for statistical analysis. The findings are synthesized to identify patterns, gaps, and evidence-based recommendations for mitigating antidepressant withdrawal syndromes. This methodological approach ensures a rigorous, transparent, and reproducible review of the existing literature.

RESULTS AND DISCUSSION

Antidepressants

Antidepressants are the first line in the treatment of anxiety and depressive disorders, used in adults within one year with an estimated prevalence of between 2,7%-15,7% (Lewer et al., 2015; Mckee & Dingee, 2003). In October 2021 and September 2022 there were 84,8 million antidepressant medications prescribed in the UK, this was an increase of 2,9 million on the previous year [11].

During 2015-2018 in the United States, 13,2% of adults used antidepressant treatment in the last 30 days, with female users accounting for 24,3%. In 2011, half of antidepressant users in the UK were on such medication for more than two years (Brody & Gu, 2020). In contrast to America, half of antidepressant users have been on the medication for at least five years (Read et al., 2023). The use of antidepressants often causes unwanted side effects, for example nausea, vomiting, and impaired sexual function. The occurrence of side effects causes patients to stop their treatment (Sørensen, Juhl Jørgensen, et al., 2022).

Abrupt discontinuation will cause withdrawal syndrome, and the prevalence of withdrawal syndrome that occurs during antidepressant treatment reaches 55,7% (Quilichini et al., 2022). Table 1 will show the antidepressant classes and examples of antidepressant drugs. Meanwhile, atypical antidepressants such as mirtazapine and agomelatine have a low risk of withdrawal syndrome (Davies & Read, 2019; Sørensen, Juhl Jørgensen, et al., 2022).

Table 1. Antidepressant classes and examples of antidepressant drugs

Antidepressant classes	Examples of antidepressant drugs
SSRI	Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Escitalopram
SNRI	Venlafaxine, Duloxetine, Desvenlafaxine, Milnacipran, Levomilnacipran
Tricyclic Antidepressants	Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline
Atypical Antidepressants	Bupropion, Trazodon, Mirtazapine, Vortioxetine, Agomelatine
Benzodiazepine	Alprazolam, Diazepam, bromazepam

Antidepressants Withdrawal Syndrome

Antidepressants that have a short half-life (≤ 24h) tend to have a higher risk of withdrawal syndrome compared to those that have a long half-life (> 24h) (Quilichini et al., 2022). Short half-life including Paroxetine, Fluvoxamine, Duloxetine, Venlafaxine, Milnacipran, Desvenlafaxine, Reboxetine, Mianserin, and Agomelatine. Whereas long half-life includes Citalopram, Escitalopram, Sertraline, Fluoxetine, Mirtazapine, and Vortioxetine (Quilichini et al., 2022). Antidepressant withdrawal syndrome as a term describes defined symptoms including somatic and psychological (Table 2) (Fava et al., 2015).

Antidepressant withdrawal can occur days, weeks, or even months after abrupt discontinuation of antidepressants and dose reduction of various types of antidepressants (Fava, 2020; Jha et al., 2018). Table 3 will explain in detail the withdrawal syndrome that occurs with

each drug. National Institute of Clinical Excellence (NICE) explained that withdrawal can sometimes be more difficult with symptoms lasting longer and withdrawal symptoms can sometimes be severe, particularly if the antidepressant medication is stopped suddenly [19]. Generally, withdrawal symptoms can be categorized into five different types, such as new symptoms (acute withdrawal symptoms), rebound, persistent post-withdrawal disorder, relapse, and recurrence (Chouinard & Chouinard, 2015).

Alternative strategies of antidepressant withdrawal include hyperbolic dose reduction. Dose reduction based on decreasing the serotonin transporter (SERT) occupancy by 10% weekly, hyperbolic dose reduction results in a linear reduction in SERT occupancy (Horowitz & Taylor, 2019; Sørensen, Ruhé, et al., 2022). Hyperbolic dose reduction schedule was used as an attempt to reduce the severity or incidence of a withdrawal syndrome (Groot & van Os, 2021). Research conducted by Galla et al (2022) on 25-year-old male patients taking 10mg escitalopram and reducing the weekly hyperbolic dose to 5mg, 3mg, 1,5mg, 1mg, 0,5mg, and 0,25mg before stopping treatment. The results obtained are withdrawal severity significantly better than previous antidepressant cessations (Gallo & Hulse, 2022).

Table 2. Common Symptoms of Antidepressant Withdrawal

Somatic	Psychologic
Flushing	Depression
Hypertension or hypotension	Nightmares
Tachycardia	Insomnia
Tremors	Anger outbursts
Visual disturbances	Nervousness
Diarrhea	Suicidal thoughts
Nausea	Mood swings
Headache	Hypomania
Fatigue	Decreased concentration
Paresthesia	Irritability
Shocklike sensations	Insomnia
Light-headedness	Anxiety
Dizziness	

Selective Serotonin Reuptake Inhibitors (SSRIs)

Over two decades, the use of selective serotonin reuptake inhibitor (SSRI) has increased rapidly. The more frequently prescribed, this is related to long-term SSRI use (Bachmann et al., 2016; Pratt et al., 2017). Selective serotonin reuptake inhibitors (SSRIs) have advanced the treatment of depression and other mental disorders. Withdrawal of SSRIs can result in a confounding of psychiatric symptoms with actual relapses or recurrence of the original disease. When discontinuing and reducing SSRI doses, withdrawal symptoms should be identified to avoid prolonging treatment or administering unnecessary high doses (Chouinard & Chouinard, 2015).

Long-term use of SSRI drugs can result in decreased regulation of serotonin receptor concentrations and decreased receptor reactivity, this can result in withdrawal symptoms if abrupt discontinuation (Bhat & Kennedy, 2017; Palareti et al., 2016). SSRI withdrawal syndrome was previously thought to last only 1 week, but some studies have stated that they may last 6 weeks [7].

New withdrawal symptoms following decrease or discontinuation of SSRI has been widely documented and include a wide range of symptoms (Cosci & Chouinard, 2020). New withdrawal symptoms include flu-like symptoms, headaches, nausea, diarrhea, dizziness, decreased concentration, sleep disturbances, dysphoria, irritability, and restlessness (Chouinard & Chouinard, 2015). Peaks of onset occur 36 hours to 10 days after dose decrease or abrupt discontinuation, they are usually reversible and last from a few hours to 6 weeks (Cosci & Chouinard, 2020).

Paroxetine is the most likely to be associated with new withdrawal symptoms, while fluoxetine being the least associated (Cosci & Chouinard, 2020). Paroxetine belongs to the SSRI group which is well tolerated and is a safe first line. Paroxetine is widely used in the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD). However, several studies report that the occurrence of withdrawal syndrome is very high in patients using paroxetine (29%-66%) when compared with other SSRIs (Murata et al., 2010).

Withdrawal syndrome due to paroxetine has been found in 35,7% by direct interview with patients. Patients who stop using paroxetine abruptly will experience withdrawal syndrome significantly more than patients who reduce the dose gradually (Murata et al., 2010). In a qualitative interview study, 29 individuals used SSRIs and experienced withdrawal in 2022, with details of the drugs are sertraline (55%), fluoxetine (30%), and paroxetine (5%). The result of this research shows that when experiencing withdrawal, the impacts felt are emotional, cognitive, and social functioning (Mahmood et al., 2024).

Online survey conducted by Read et al, participants who used fluoxetine (19,4%), sertraline (15,2%), paroxetine (9,7%), and escitalopram (8,1%) shows that paroxetine is higher can cause adverse effects and withdrawal than the others (Read & Williams, 2018). While an online survey in 2019, participants who used paroxetine (n=59), fluoxetine (n=111), escitalopram (n=48), and sertraline (n=102) showed that paroxetine could cause withdrawal symptoms were higher than the others (74,6%). Withdrawal symptoms were suicidality, insomnia, and sexual dysfunction (Read, 2020).

A smaller but valuable analysis, of 110 postings on an antidepressant website, found that 94% reported one or more psychological withdrawal effects (brain fog, anxiety, depression, feeling suicidal, irritable, emotional numbness); 66% reported neurological effects (dizziness); less than 43% reported one or more of the following gastrointestinal effects (nausea, bloated, diarrhea, constipation, sensitivity to food). The average duration of withdrawal symptoms among SSRI users was almost 21 months, and for SNRI users it was nearly 12 months. Fifty percents SSRI users experienced symptoms lasting 7,8 months or more, and 25% symptoms at least 2 years. Meanwhile, 50% SNRI users, symptoms lasted at least 6,4 months, and 25% for 14,4 months or more (Stockmann et al., 2018).

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin and norepinephrine reuptake inhibitors (SNRIs) additionally affect both serotonin and NE, they can improve symptoms of depression including decreased concentration, physical slowing, and decreased selfcare (Bruno et al., 2016). Venlafaxine has the shortest half-life at an average of 5 hours and greater reports of withdrawal symptoms [7]. Some negative side effects of SNRIs include possible increased blood pressure and heart rate,

especially with levomilnacipran (Bruno et al., 2016). Withdrawal symptoms such as headache, lethargy, diaphoresis, tachycardia, hypertension or hypotension, mood swings, suicidal thought, and insomnia [7].

Desvenlafaxine is an SNRI for the treatment of adults with major depressive disorder (MDD) (Nichols et al., 2010). This randomized, double blind, placebo-controlled study compared withdrawal symptoms based on *Discontinuation Emergent Signs and Symptoms* (DESS) scores between abrupt discontinuation of desvenlafaxine 50mg and tapering dose of desvenlafaxine 50mg to 25mg. The results of this research are that the DESS scores of the double-blind taper dose and abrupt discontinuation are not too different. The score for taper dose is 4,8 and abrupt discontinuation is 5,3. Abrupt discontinuation of long-term use of desvenlafaxine 50mg/day does not increase the occurrence of withdrawal symptoms compared with 1-week taper dose to 25mg/day (Khan et al., 2014).

Abrupt discontinuation more frequently reported adverse effects (51%) compared with taper dose (39%). The most common adverse effects in the current study, include nausea, headache, and dizziness (Khan et al., 2014). Stockmann et al (2018) analyzed a sample of posts on an antidepressant withdrawal website report experienced persistent post-withdrawal disorders with neurological symptoms more common among SNRI users [34]. Episodes of long duration of withdrawal symptoms (depression, anxiety, mania, tinnitus, nausea, unexplained fear, and dizziness) were described after SNRIs discontinuation, suggesting the occurrence of persistent post-withdrawal disorders [29], (Hou & Lai, 2014).

Persistent sexual side effects after SNRIs and SSRIs discontinuation have been identified as a syndrome called post-SNRI and SSRI sexual dysfunction (PSSD). That is characterized by a decrease or absence of libido, genital anesthesia, and orgasmic disorders and by psychological symptoms such as anhedonia, difficulty in concentrating, memory problems (Bala et al., 2018; Healy et al., 2018). It has been described the case of a patient in which PSSD symptoms were part of a broader syndrome which was diagnosed as persistent post-withdrawal disorder. This case raises the suspicion that PSSD might be a withdrawal syndrome occurring after decrease or discontinuation of SNRIs (Healy et al., 2018).

Hengartner et al (2020) conducted research using an internet forum called SurvivingAntidepressants.org. This internet forum is for people tapering psychiatric drugs or recovering from antidepressant withdrawal syndromes. From this study, there were 20 people who used SNRIs, including duloxetine (n=2), venlafaxine (n=17), and desvenlafaxine (n=1). Venlafaxine was implicated in 80% of protracted withdrawal syndrome (PWS) case. The most common symptoms were headache, fatigue, dizziness, and brain zaps (Hengartner et al., 2020). Protracted withdrawal syndrome (PWS) which lasts much longer, from months to years (Baldessarini & Tondo, 2019).

Tricyclic Antidepressants (TCA)

Although the mechanism of action of TCAs is not completely understood, therapeutic benefit likely comes from inhibition of serotonin and NE reuptake transporters and blockade of alpha-1 and alpha-2 adrenergic, muscarinic, and histamine postsynaptic receptors (Hillhouse & Porter, 2015). Side effects from TCAs result from their action at muscarinic and histamine receptors. Because of their activity on the previously mentioned receptors, withdrawal

symptoms can range from headache, nausea, sleep changes, and restlessness to the development of mania or hypomania (Hillhouse & Porter, 2015).

Atypical Antidepressants

Vortioxetine is an atypical antidepressant that acts as a multimodal serotonin modulator and stimulator. Vortioxetine acts as a selective serotonin reuptake inhibitor, a serotonin receptor agonist at 5-HT1A, a partial agonist at 5-HT1B, and an antagonist at 5-HT3a, 5-HT7, and 5-HT1D (Alvarez et al., 2014; Pompili et al., 2014). A randomized, double-blind, study showed that vortioxetine was superior to agomelatine in patients with MDD who had an inadequate response to SSRI or SNRI treatment who desired to switch therapy. Vortioxetine shows a lower withdrawal rate than agomelatine (Papakostas et al., 2018; Thase et al., 2017).

Meanwhile, bupropion has inhibitory properties on both NE and dopamine reuptake and acts as a central nervous system stimulant. Although bupropion does not require a tapering dose, a case report reported that withdrawal symptoms due to bupropion may occur [5].

Benzodiazepine

Benzodiazepines are a highly effective psychoactive drug with anxiolytic, hypnotic, muscle-relaxant, and anticonvulsant properties. Benzodiazepines are most used to treat symptoms of anxiety and insomnia (Dell'osso & Lader, 2013). The average prevalence of long-term benzodiazepins use between 25-76%. Around 20-50% of benzodiazepins believe they have experienced withdrawal when trying to stop (Liebrenz et al., 2015). The most frequent minor new withdrawal symptoms are sweating, tachycardia, nausea, visual changes, tremors, confusion, restlessness (Malcolm & Andri, 2016).

New withdrawal symptoms are generally mild, transient, and subside within 2-4 weeks. More new withdrawal symptoms were found upon discontinuation of lorazepam (high potency and short acting) than with diazepam (Carvalho et al., 2016; Cloos et al., 2015). Benzodiazepines are over prescribed in treatment resistant depression (TRD). Despite recommendations for withdrawal and psychiatric follow-up, less than 5% of patients successfully stopped taking benzodiazepines at one year (Fond et al., 2023).

Rebound insomnia was found to be significantly lower in all benzodiazepines compared to triazolam (Cloos et al., 2015). Short and intermediate elimination half-life benzodiazepines are at a greater risk of rebound anxiety compared to long elimination half-life agents. Clonazepam has a long elimination half-life, induced less frequently rebound anxiety than alprazolam (Lejoyeux et al., 2015; Nardi, 2018; Starcevic, 2014).

Table 3. Withdrawal Symptoms of Each Drugs

Author	N (population)	Drug	Withdrawal Symptoms
Gallo, A. and Hulse, G	1 participant	Escitalopram	Mood swings, fatigue, burning, numbness, tingling sensations, and diarrhea [24]
Lejoyeux, M., Matharan, S. and De Bodinat, C	315 participants	Agomelatine, paroxetine, and venlafaxine	Headache, nausea, dizziness, diarrhea, anxiety, vomiting, insomnia, irritability, vision blurred, depression,

Author	N (population)	Drug	Withdrawal Symptoms
			nervousness, agitation (Lejoyeux et al., 2015)
Papakostas, G.I. *et al*	362 participants	Desvenlafaxine	Headache, nausea, dizziness, coronary artery disease, dehydration, arthritis, muscle twitching, dyspnea, intentional self-injury, and suicidal thought [46]
Nakagome, K. *et al*	161 participants	Escitalopram and duloxetine	Cold, sleepiness, diarrhea, headache, nausea, constipation, and flu (Nakagome et al., 2021)
Durgam, S. *et al*	891 participants	Levomilnacipran	Nausea, headache, heart rate increased, constipation, hyperhidrosis, erectile dysfunction, dizziness, tachycardia, upper respiratory tract infection, dry mouth, blood pressure increased, insomnia, and nasopharyngitis (Durgam et al., 2019)
Murata, Y. *et al*	56 participants	Paroxetine	Dizziness, increased dreaming or vivid dreams, fatigue, nausea or vomiting, headache, anxiety, paresthesia, insomnia, diarrhea, visual disturbance, fever, tremor, irritability, and chills [30]
Guy, A. *et al*	158 participants	Venlafaxine	Mood totally unstable and migraine pain (Guy et al., 2020)
Hengartner, M.P. *et al*	69 participants	Sertraline, venlafaxine, escitalopram, paroxetine, and fluoxetine	Headache, fatigue, dizziness, brain zaps, tremor, sweating, nausea, and diarrhea [41]
Read, J., Cartwright, C. and Gibson, K	1829 participants	Paroxetine, venlafaxine, and fluoxetine	Feeling emotionally numb, sexual difficulties, and suicidality (Read et al., 2014)
Read, J	867 participants	Paroxetine, venlafaxine, fluoxetine, escitalopram, and sertraline	Anxiety or panic, irritability, dizziness, brain zaps, nightmares, and nausea [33]
Liebrenz, M. *et al*	41 participants	Benzodiazepine	Irritability, nervousness, restlessness, difficulty sleeping, tickling sensations, and loss of appetite [49]

Author	N (population)	Drug	Withdrawal Symptoms
Cartwright, C. *et al*	180 participants	Venlafaxine, paroxetine, and fluoxetine	Reduced positive feelings, suicidality, and feeling not like myself (Cartwright et al., 2016)
Fixsen, A.M. and Ridge, D	500 participants	Benzodiazepine	Weak, chills, sweats, bodily pains (Fixsen & Ridge, 2017)

CONCLUSION

Antidepressants with a short half-life, such as paroxetine, venlafaxine, desvenlafaxine, agomelatine, and benzodiazepines, are most commonly associated with withdrawal symptoms, which can emerge days to months after abrupt discontinuation or rapid dose reduction. These withdrawal effects highlight the need for effective management strategies, including alternative approaches like hyperbolic dose reduction to minimize patient discomfort and health risks. Future research should focus on comparing the long-term effectiveness and safety of different tapering protocols across diverse patient populations to establish best practices for antidepressant withdrawal management.

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