REVIEW ARTICLE

Differential Withdrawal Symptoms of Typical and Atypical Antipsychotics: A Narrative Review

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Abstract

Antipsychotics (APs) reduce abnormal neurotransmitter activity and treat mental conditions. However, APs can cause withdrawal symptoms, which can disrupt normal physiology. This research aimed to evaluate the APs' withdrawal symptoms and their evidence-based management. In the current review, forty-six papers were included after careful evaluation. All studies comparing the withdrawal symptoms between typical and atypical APs were included, while those focusing solely on safety were excluded. Quality and strength of evidence were also evaluated by standardised criteria. Abrupt discontinuation of typical APs results in dopaminergic rebound, causing motor symptoms. The aberrant discontinuation of atypical APs results in rebounds of dopaminergic, serotonergic, and cholinergic systems, leading to emotional dysregulation. Withdrawal symptoms must be managed by considering individual drug mechanisms as well as the demographics of patients. Clozapine withdrawal is associated with fewer side effects when tapered gradually over six months; risperidone discontinuation requires careful monitoring for dose-dependent extrapyramidal symptoms. Adolescents using olanzapine exhibit higher withdrawal-related morbidity compared to other age groups. Prolonged tapering of quetiapine has been shown to effectively mitigate withdrawal symptoms. Patients discontinuing aripiprazole experience mood swings due to its partial agonist effects on dopamine receptors; abrupt discontinuation of ziprasidone can lead to rebound psychosis and increased anxiety. The discontinuation of APs over a prolonged period shows improved patient outcomes; however, the period for discontinuation should be tailored to the individual patient's needs and the medication used. A holistic approach to tapered discontinuation can improve medical and psychosocial outcomes.

Keywords: *Typical-antipsychotics, atypical-antipsychotics, withdrawal, symptoms, dopamine-receptor, serotonin-receptor.*

INTRODUCTION

Antipsychotics (APs) are indicated to treat psychotic illnesses; these illnesses are usually accompanied by hallucinations and delusions [1, 2]. In addition, antipsychotic drugs are also indicated to treat a wide range of other mental conditions, including agitation in neurodegenerative disorders, psychotic depression, and bipolar affective disorder [3, 4]. According to research analysis, around 75% of patients discontinue the use of their antipsychotic medications within 18 months [5]. However, to control side effects, people usually self-regulate and alter the doses of their antipsychotic medications. Furthermore, antipsychotic drugs are categorised into two classes: typical (*e.g.*, chlorpromazine, trifluoperazine, thioridazine, perphenazine, fluphenazine, thiothixene, haloperidol, molindone, loxapine) and atypical (*e.g.*, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, lurasidone). Typical APs block dopamine, while atypical ones have effects on both serotonin and dopamine, but the effects of dopamine are not as strong as those of typical antipsychotics [6, 7]. Except for clozapine, it seems appropriate to administer typical or atypical antipsychotics in the treatment of acute psychoses as well as in the maintenance treatment of schizoaffective and schizophrenia disorders [5]. The first generation (typical) APs do better at combating the more simplistic schizophrenia, more specifically delusions and hallucinations [7]. In opposition, the second generation (atypical) APs minimise relapses and address positive and negative symptoms of the illness, such as ambivalence and withdrawal [6, 7].

Unfortunately, the withdrawal symptoms can often resemble a worsening of the underlying mental condition when antipsychotics are withdrawn [5]. There are several examples of such symptoms, including autonomic instability, motor abnormalities, and rebound psychosis [6]. There are claims that about 40% of patients experience antipsychotic withdrawal symptoms, which underscores therapeutic or non-therapeutic understanding and management of these symptoms [5]. Akathisia and withdrawal dyskinesia are the motor symptoms that are prominent in the withdrawal pattern of common typical antipsychotics [7]. Research suggested that in the case of abrupt cessation of drugs like typical antipsychotic drugs like fluphenazine or haloperidol, there could be a large dopaminergic surge, resulting in uncontainable movements and a reinstatement of psychoses [8]. Apart from the withdrawal phase, symptoms like tachycardia, sweats and gastrointestinal upset are also apparent [9].

Although second-generation APs are more effective than first-generation APs, they are less likely to result in involuntary changes as well as side effects (especially

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motor ones) [8, 10]. According to one study, upon withdrawal, these drugs could cause anti-cholinergic rebound, insomnia and alterations of mood stability [8]. For example, salivation, diarrhea and extreme levels of anxiety render the sudden discontinuation of clozapine [9]. Similarly, APs that have high serotonergic activity, such as atypical antipsychotic olanzapine, are more likely to result in poor control of emotions and increased frequency of depressive episodes after cessation [10].

On the contrary, first-generation (typical) antipsychotic medications are most effective when they block the dopamine (D2) receptors in the brain's basal ganglia [9]. Ultimately, long-term therapy leads to dopamine receptor upregulation when the brain develops more dopamine receptors or makes existing ones more effective in response to reduced dopamine function [11]. It is analysed that dopamine enables excess transmission of the sensitive receptors when medication is stopped, resulting in dopaminergic hyperactivity [12]. The use of atypical antipsychotics is a classical explanation of the tolerance phenomenon, as medications lose effectiveness over time [13]. Withdrawal from atypical APs involves more complex interplay between the dopaminergic, serotonergic and cholinergic systems that results in emotional and autonomic dysfunction [14]. In contrast, typical AP withdrawal primarily manifests as dyskinesia and delusions due to dopaminergic action [11].

Therefore, designing individualised cessation protocols, a cross-comparative study is required owing to the different antipsychotic-type characteristics and withdrawal symptoms. Hence, the current review aimed to expand on the literature on the withdrawal symptoms of APs and provided the necessary differences that must be considered concerning their pathogenesis, clinical course, manifestations and therapy. The review may provide practitioners with useful recommendations supported by the findings of the latest clinical studies, which hopefully would qualify the withdrawal of antipsychotics as a safer and more effective procedure.

METHODOLOGY

Study Design: This article examined the differences in withdrawal symptoms between typical and atypical APs using a narrative review methodology. The study thoroughly compares the withdrawal symptoms of these two classes of medications by synthesising results from recent observational studies and clinical trials.

Search Strategy: This study used PubMed, BioMed Central, PsycINFO, National Database of Indian Medical Journals, African Journals Online (AJOL) and Google Scholar for searching the literature. Typical APs discontinuation, typical and atypical APs withdrawal, antipsychotic withdrawal symptoms and antipsychotic cessation are the keywords utilised in this literature search. To guarantee that current APs and pertinent withdrawal information are included, the search concentrated on papers published in peer-reviewed journals within the last 15 years (2010 to 2024). A structured literature search was performed to retrieve the relevant studies for preparation of this manuscript. Out of total 77 identified record, finally 24 papers were studied for producing this narrative review (**Fig. 1**) [15].

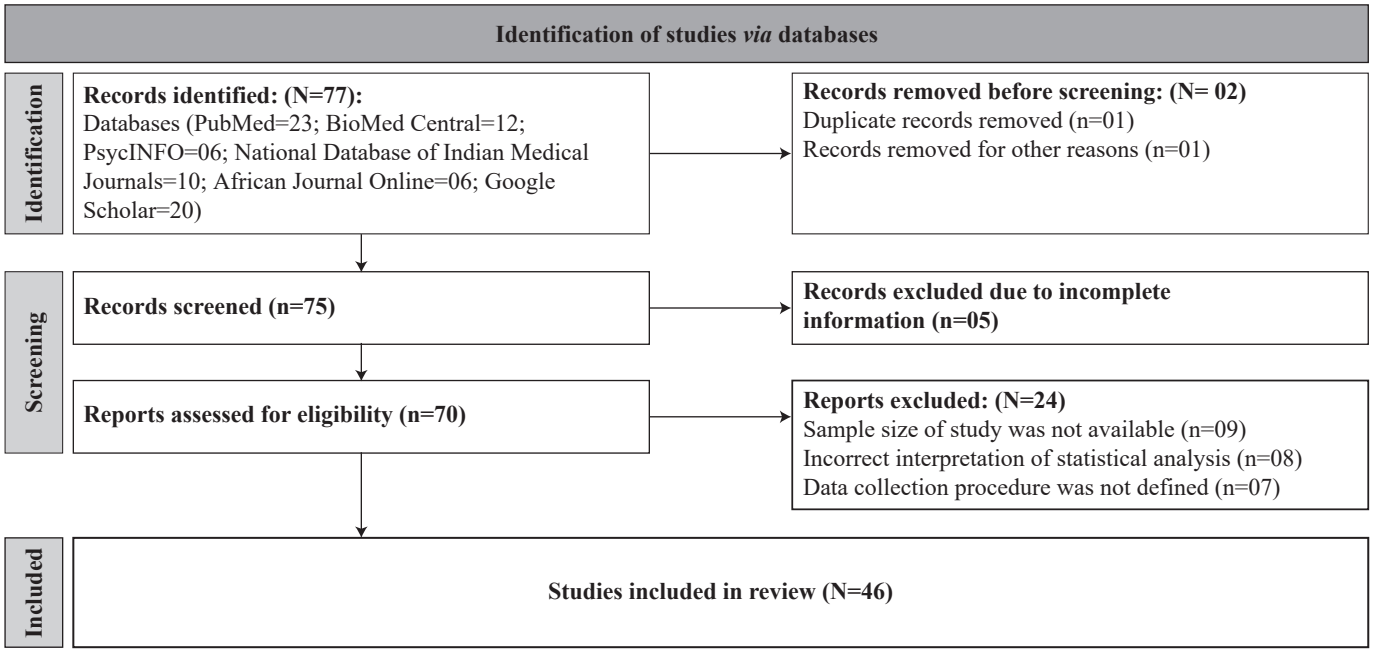

Fig. (1): A flow diagram depicting systematic literature search and selection of studies.

Inclusion and Exclusion Criteria: Studies comparing withdrawal symptoms in patients stopping conventional and atypical APs, clinical research on humans, observational studies, case studies, and meta-analyses about antipsychotic withdrawal symptoms were included. However, research that concentrates on antipsychotic safety or efficacy but ignores withdrawal symptoms is excluded. Papers that focus on experimental APs but are not authorised for clinical use or animal research are also excluded from the study. Those articles or research analyses written in a language other than English were also excluded.

Study Selection and Data Extraction: The studies were selected based on selection criteria and evaluated for eligibility, and ultimately added to this article. Two separate reviewers screened all identified articles' titles and abstracts. Potentially eligible studies' full texts were retrieved and thoroughly evaluated.

Data Compilation and Analysis: To evaluate withdrawal symptoms between typical and atypical APs, the retrieved data were combined. The main conclusions are described, such as the kinds of withdrawal symptoms, how long they last and how they affect patients. Quality of the literature was determined by GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria [16].

FINDINGS AND DISCUSSION

Table **1** summarises the differences in withdrawal symptoms between typical and atypical APs. Each study was evaluated for its objectives and outcomes [17-30]. Table **2** summarises the withdrawal strategies based on the literature evaluated.

Antipsychotics (APs) have withdrawal symptoms when discontinued, and these withdrawal symptoms vary between typical and atypical APs. The abrupt discontinuation of typical APs resulted in a dopaminergic rebound, causing motor symptoms like dyskinesia and akathisia along with psychotic relapses resembling the primary illness [31]. However, the aberrant discontinuation of atypical APs resulted in rebounds of dopaminergic, serotonergic, and cholinergic systems [32]. Thus, the spectrum of withdrawal symptoms is broader in patients treated with atypical APs and symptoms included mood dysregulation, sweating, gastrointestinal upset, hyper salivation and increased anxiety [33].

Although atypical APs have more withdrawal symptoms, on the other hand, they have superior safety and efficacy profiles compared to typical APs [7]. This review presented strategies to manage the withdrawal symptoms of atypical APs effectively. For instance, studies have shown that extending the withdrawal period over one month reduced the risks of primary symptoms relapse and neuroadaptive responses [34, 35]. Additionally, the management of withdrawal symptoms ought to be differentiated according to the specific medications being used. For instance, the hazards associated with withdrawal from clozapine are negligible when the medication is stopped gradually over six months [36, 37]. Risperidone is associated with dose-dependent extra-pyramidal symptoms, necessitating thorough patient screening for motor symptoms throughout the cessation process [31]. These findings are consistent with another review article written by Horowitz *et al*. [38]. To minimise withdrawal symptoms and ensure long-term stability for patients, it is essential to develop discontinuation protocols for certain Aps [39, 40].

Furthermore, managing withdrawal symptoms varied according to demographic parameters [41]. For instance, Merino *et al*. reported atypical APs misuse and withdrawal-related morbidity linked to drugs like quetiapine and olanzapine among adolescents [18]. Therefore, practitioners must carefully consider the sensitivity of treatment plans for withdrawal symptoms management as per patient age [42]. The decision to stop APs could add to the chances of relapse; this could be associated with dopaminergic hypersensitivity that remained even after the treatment has been withdrawn [43]. Therefore, a gradual tapering of APs would be beneficial in reversing the dependency and reducing the possibility of a relapse after stopping the medications [44, 45].

In addition, based on animal studies, observations of tardive dyskinesia, and the temporal clustering of relapse events, there is a risk of transition to the chronic state that remains after stopping the medication [41]. However, atypical APs do not affect tardive dyskinesia and the temporal clustering in drug-naive patients. Atypical drugs increase temporal clustering volume in the thalamus and cortex [46]. This suggested that structural changes from schizophrenia may be reversed with atypical drugs. Due to this reason, in treating schizophrenia, a significant expectation has been raised for atypical APs over typical APs [47]. According to one study, 585 people experienced withdrawal antipsychotic symptoms; of which 72% of participants reported anxiety, anxiousness, headaches, nausea, shivering, and other symptoms, which are medically referred to as classical withdrawal syndrome [19]. An additional 52% of the same patients later indicated that

Table 1: Difference between withdrawal symptoms of typical and atypical antipsychotics.

Author first name	Year	Study design	Study participants	Study objective	Study outcomes/conclusion	Quality	Reference
de Kuijper,	2022	Qualitative study	250 physicians of different specialities prescribed APs with varied experience of withdrawal symptoms in their patients	The study aimed to explore the experiences of individuals associated with mild intellectual disabilities after discontinuing long-term antipsychotics; these include challenging behaviour, underscoring factors influencing success and the need for their involvement in decision-making.	Successful atypical (clozapine, risperidone) and typical antipsychotic (chlorpromazine) discontinuation for people with mild disabilities specifically relies on clear communication, supportive networks and accessible healthcare and coping abilities. However, educating healthcare providers is the key to enhancing decision-making and support.	High	[17]
Malla, A.	2022	Observational study	253 patients; 107 patients of varied ages discontinued the medication.	The study aimed to examine the effects of discontinuation of antipsychotics, specifically on clinical and functional outcomes in individuals with first-episode psychosis in two different cultural environments	Discontinuation of atypical antipsychotic medications, *e.g.*, clozapine, quetiapine, risperidone, after the management of the first episode of psychosis could be facilitated by patient-specific characteristics that mitigate the negative consequences.	Low	[5]
Merino, D,	2022	Pharmaco-vigilance study	1023 patients aged 12 to 17 years old; quetiapine (n=368), risperidone (n=224), aripiprazole (n=129), and olanzapine (n=118). 65 Patients aged 2-11 years old. Dyskinesia (n=16), dystonia (n=13), and aggression (n=11)	The study aims to investigate patterns of antipsychotic use and withdrawal in children and adolescents utilising WHO pharmacovigilance data.	Adolescents who intentionally misuse atypical antipsychotics, especially quetiapine, olanzapine, risperidone, and aripiprazole, have been associated with withdrawal symptoms. A thorough evaluation of symptoms can reveal side effects linked to antipsychotics, directing proper treatment and lowering morbidity.	Moderate	[18]
Read, J.	2022	Cross-sectional study	585 patients with varied age groups. 72% with classic withdrawal symptoms; 26% positive symptoms; 18% reported psyvhosis	The study aims to investigate the withdrawal symptoms experienced by antipsychotic users and inform prescribers' practices to support medication discontinuation.	The type and severity of atypical antipsychotic, *e.g.*, ziprasidone, quetiapine, clozapine and olanzapine withdrawal symptoms, such as withdrawal psychosis, must be understood by prescribers. To stop patients from suffering during withdrawal, updated protocols and assistance are crucial.	High	[19]
Larsen-Barr, M	2021	Qualitative descriptive study	Female patients 18 years and above; discontinued AP medications in New Zealand. Relapse after discontinuation in 3 months to 1 year.	This study aims to explore how individuals successfully discontinue antipsychotic medication and maintain well during and after withdrawal, and concerning the strategies and internal resources they utilise.	The study concluded that successful discontinuation of atypical antipsychotic drugs, *e.g.*, clozapine, olanzapine and risperidone, is possible, specifically with gradual withdrawal strategies and a focus on maintaining rather than avoiding relapse.	Low	[20]

Author first name	Year	Study design	Study participants	Study Objective	Study outcomes/conclusion	Quality	Reference
Deb, S	2020	Questionnaire-based survey	16 adult participants of the study. Evaluated for withdrawal symptoms of drugs. Intellectual disability was the main issue reported by all participants.	The purpose of the study was to explore the perspectives of psychiatrists, specifically on the successes and challenges of withdrawing antipsychotics for individuals with intellectual disabilities, specifically in light of the STOMP (Stopping Overmedication of People) initiative.	The study underscores the need for national guidelines to facilitate systematic psychotropic drug reviews and withdrawal of atypical antipsychotic drugs, *e.g.*, clozapine, quetiapine and olanzapine for individuals associated with intellectual disabilities.	Moderate	[21]
Chiappini, S,	2020	Observational study	379 male, 171 female patients aged 18-65 years. 2 adolescents.	The study aims to focus on clozapine withdrawal and misuse-related cases that were reported to the European Medicines Agency's pharmacovigilance database.	EMA data analysis highlights atypical antipsychotic drug clozapine withdrawal as a significant concern; they are linked to misuse, abuse, or withdrawal. The prevalence of overdose and fatalities (n=46) in substance abuse emphasises the need for research on clozapine discontinuation.	Low	[22]
Kleijwegt, B,	2019	Mixed-method study	29 adult participants (22 female) of different organisations using APs. Mean age 44 years. All complaints for behavioural issues due to the use of APs.	The purpose of this study is to investigate staff perception of discontinuing antipsychotics, particularly in residential clients associated with intellectual disabilities, concerning their willingness and attitude regarding the process.	It is concluded that promoting staff positive attitude and structured reduction plans are important parameters, as they help in managing discontinuation of atypical antipsychotic drugs, *e.g.*, risperidone, in residential clients associated with intellectual disabilities. Therefore, a tailored approach is required for withdrawal.	High	[23]
Taipale, H,	2018	Retrospective cohort study	61889 Finnish patients, mean age 46.2 years (50.3% male), 29823 Swedish patients, mean age 44.9 years (57% male).	The study aims to investigate the impact of antipsychotic discontinuation on treatment failure and survival in schizophrenia, using nationwide register data to analyse outcomes over time.	The findings of the study reported that relapse risk was reduced specifically after discontinuing atypical antipsychotic drug use, *e.g.*, quetiapine and olanzapine. However, the study shows that relapse risk remains steady during the disease while long-term antipsychotic use is associated with enhanced survival. Gradual withdrawal is required with continuous monitoring of symptoms of relapse.	High	[24]
Emsley, R,	2018	Randomised placebo-controlled trials	The total sample size of the study was 133 adults. A withdrawal duration of less than 52 weeks was not successful for the cessation of AP therapy.	The study aims to investigate whether relapse after discontinuation of antipsychotics is due to illness recurrence or withdrawal phenomenon.	The study findings suggest that relapse after treatment discontinuation of atypical antipsychotic drugs, *e.g.*, quetiapine, risperidone, clozapine and typical antipsychotic drugs, *e.g.*, chlorpromazine, is linked to illness reoccurrence and the role in psychosis. No evidence supporting withdrawal as a cause in 52 52-week duration of dose tapering and gradual withdrawal.	Moderate	[25]

Author first name	Year	Study design	Study participants	Study objective	Study outcomes/conclusion	Quality	Reference
Ostrow, L.,	2017	Cross-sectional survey	250 US adults >18 years (158 female, 41 male, 5 transgender, 3 self-identified, 43 not identified) diagnosed with mental illness.	The study aims to explore the experiences, strategies, and outcomes of long-term psychiatric medication discontinuation among US individuals, underscoring challenges and supports in the process.	Withdrawal of psychiatric drugs, *e.g.* atypical antipsychotic drugs quetiapine, clozapine and typical antipsychotic drug chlorpromazine, is challenging; however, most participants are satisfied with the decision by counselling and friend support. Future research will help medical professionals better support patients, specifically in managing medication use and discontinuation.	Low	[26]
Sarma, S.	2016	Case report	Female patient, 18 years of use of clozapine. 5 days of clozapine discontinuation led to severe withdrawal symptoms.	The study aims to report a case of psychotic decompensation, oculogyric, and axial dystonia due to abrupt clozapine withdrawal and discuss underlying mechanisms and the importance of early reinstitution of clozapine.	The study presents a unique case of psychotic decompensation, oculogyric crises, and limb axial dystonia due to abrupt atypical antipsychotic clozapine withdrawal. Early recognition and prompt reinstitution of clozapine are significant in preventing the recurrence of withdrawal symptoms.	High	[27]
Landolt, K,	2016	Randomised controlled trial	325 adult patients with schizophrenia from Europe and Israel.	This study aims to investigate the effects of discontinuation of antipsychotic medication, *e.g.*, chlorpromazine, clozapine, and olanzapine, on outcomes in the European First Episode Schizophrenia Trial (EUFEST)	Clinical, regional, and social factors influenced the success of the discontinuation. More research is required to determine predictors of successful discontinuation due to relapse and adverse outcomes after withdrawal.	Low	[28]
Azermai, M,	2013	Clinical observational study	40 hospitalised geriatric patients. Mean age 84 (67-95) years.	The study objective is to investigate the effects of abrupt antipsychotic discontinuation, specifically in cognitively impaired older persons.	Abrupt typical antipsychotic (*e.g.*, haloperidol) and atypical antipsychotic (*e.g.*, quetiapine, risperidone) discontinuation may be viable, specifically in older patients with behavioural and psychological symptoms, because of less serious withdrawal symptoms. Systematic efforts are required to identify those who benefit *versus* those for whom the benefits outweigh the risks.	Moderate	[29]
Cerovecki, A,	2013	Qualitative study	208 *in vitro* and *in vivo* studies of binding affinities of dopamine, serotonin, alpha, histamine and acetylcholine receptors and their related adverse effects and withdrawal symptoms.	The study aims to examine the pharmacological mechanism and withdrawal symptoms that are associated with discontinuing atypical antipsychotics, *e.g.*, clozapine and risperidone, while offering practical recommendations for clinicians.	The research study highlights the pharmacological profiles of atypical antipsychotic drugs and underscores the need for future research to guide safe discontinuation and switching strategies.	Moderate	[30]

Table 2: Withdrawal strategies based on the literature evaluated.

Drug	Class	Strategy
Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, Paliperidone, Asenapine, Iloperidone, Lurasidone	Atypical (Second generation) antipsychotics	1. Confirm that the symptoms of psychosis are completely resolved. 2. Patient should not have had any symptoms of disease for the last 6-12 months. 3. Evaluate the risk and benefit of withdrawal in each patient. 4. Taper the dose down 10% to 25% per week. 5. Monitor the symptoms, *e.g*., insomnia, anxiety, irritability or relapse of psychotic symptoms. 6. Switch to a half-life drug like Quetiapine before tapering completely. 7. Support therapy with benzodiazepine for anxiety and mood stabilisers or antidepressants for other symptoms. 8. Cognitive behavioural therapy and counselling should be incorporated into the plan. 9. Plan for relapse prevention by restarting the same medication or drug from another class.
Chlorpromazine, Trifluoperazine, Thioridazine, Perphenazine, Fluphenazine, Thiothixene, Haloperidol, Molindone, Loxapine	Typical (First-generation) antipsychotics	1. Confirm that the symptoms of psychosis are completely resolved. 2. Patient should not have a remission period of at least 1 to 2 years. 3. Taper the dose down 10% to 25% per week, and if the drug has high potency (*e.g*., Haloperidol), then taper with a 3 to 6-month duration. 4. Monitor the symptoms, *e.g*., insomnia, anxiety, irritability or relapse of psychotic symptoms. 5. Support therapy included short half-life atypical antipsychotic, *e.g*., quetiapine or aripiprazole. 6. Benztropin can be given to prevent dystonia and Parkinsonism, and beta-blockers for akathisia. 7. Cognitive behavioural therapy, counselling and family support should be incorporated into the plan. 8. Plan for relapse prevention by restarting the same medication or drug from another class.

the tremors had started, which made their withdrawal worse [19]. Furthermore, 23% had waited at least a year before quitting entirely, and 26% had tried to quit for four or more years [19]. When asked an open-ended question about side effects, 73% of participants said they had experienced insomnia and anxiety or panic attacks [19]. 26% said they had more energy and were thinking more clearly, while 18% said they were experiencing anxiety or panic attacks [19].

There have been limited clinical trials exploring the withdrawal dynamics of APs. The available studies predominantly focused on short-term withdrawal outcomes, while limited exploration of long-term implications exists. Additionally, the evaluation of the psychological impact of withdrawal symptoms, such as emotional dysregulation, with the use of atypical APs has been scarce.

CONCLUSION

The withdrawal symptoms of typical and atypical APs have distinct mechanisms resulting in varied neuroadaptive responses as well as post-withdrawal complications. Atypical APs have higher emotional dysregulation post-withdrawal, while typical APs have higher motor symptoms. Discontinuation of APs over a prolonged period has shown improved patient outcomes; however, the period for discontinuation should be tailored to the individual patient's needs and the medication used. A holistic approach to tapered discontinuation can improve medical and psychosocial outcomes among patients using APs.

RECOMMENDATIONS

Future research should explore the long-term management of withdrawal symptoms from antipsychotic drugs. Furthermore, clinical trials should explore the integration of adjunctive therapies to manage withdrawal symptoms effectively. Clinical practitioners should offer tailored medication management during discontinuation by considering the patient's medication history, underlying mental health conditions and the specific withdrawal profiles of the APs being used.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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