

Withdrawal, Side Effects and Exacerbation of Symptoms by Antipsychotic Use for the Treatment of Schizophrenia

Akshaya Solanki

Abstract

Antipsychotics are widely used in clinical practice to reduce psychotic symptoms caused by schizophrenia. However, they might contribute to potential threats such as causing side effects, its improper management causing withdrawal and sometimes even worsening the symptoms. This review focuses on various side effects caused by antipsychotics on our physical, psychological, social, immunological and our neurobiological systems. Further, we talk about modifications in antipsychotic practice such as abrupt switching and increasing dose causing worsening of these symptoms and other side effects. Tapering and combining antipsychotics is considered as potential methods to prevent these external harmful effects.

Keywords: Antipsychotics, OCS, exacerbation, schizophrenia, Withdrawal, depression, tapering

Introduction

Schizophrenia is a chronic and severe mental disorder that significantly impacts the lives of those affected, with symptoms such as hallucinations, delusions, disorganized speech and behavior, and cognitive impairments (Radó, 2010)[1]. Antipsychotics have become rather common for treatment of psychotic disorders such as schizophrenia as they stabilize mood and reduce psychotic symptoms. Typical and atypical antipsychotics are quite common with one targeting dopamine receptors while the other having a more broader mechanism which targets dopamine as well. Antipsychotics are used as a long-term strategy to prevent relapse as well as manage chronic symptoms. While antipsychotic medications are commonly used to manage this condition, their use is not without its challenges, causing patients to experience withdrawal effects, side effects, and even a potential exacerbation of symptoms. Evidence suggests that family members of individuals with schizophrenia experience significant stress in coping with the unpredictable, frightening, and disturbing behaviors associated with the disease, which severely impact quality of life and often lead to relapse and poor illness (Aubeeluck & Luximon-Ramma, 2020)[2].

When taken as prescribed, antipsychotic medication can be an effective treatment for people experiencing distressing psychotic symptoms (Bressington et al., 2008)[3]. However, many patients find it difficult to adhere to their medication regimen consistently, and the cessation of antipsychotic drugs can result in a higher incidence of relapse compared to those who continue their treatment as prescribed (Bressington et al., 2008)[3]. For example, relapse is observed in 70% of non-adherent clients, as opposed to 20-30% for adherent clients (Bressington et al., 2008)[3]. Furthermore, non-adherence to antipsychotics has been linked to a range of negative outcomes, including poorer clinical prognosis, increased healthcare utilization and costs, and a heightened risk of aggressive or violent behaviors. Antipsychotic relapse is influenced by a variety of factors such as discontinuation of medication, improper dosage management, insufficient treatment of negative symptoms and even change in antipsychotics. Sudden

cessation of antipsychotic medications may result in withdrawal symptoms such as nausea, vomiting, insomnia, and a possible worsening of psychotic symptoms. Antipsychotic side effects can range from extrapyramidal symptoms, cardiovascular effects, anticholinergic effects etc. These side effects can vary depending on the type of antipsychotic used (typical and atypical). If not treated accordingly, antipsychotics can have adverse effects on the physical and mental being of the patient. Symptoms need to be monitored properly and appropriate treatment plans with proper dosage regulations are required to prevent the potential threats caused by antipsychotics.

Withdrawal, Side effects and Exacerbation of Symptoms

CLAMORS study found that the prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics is considerably high. One or more negative symptoms were present in 57.6% of the patients evaluated. (CLAMORS Study Collaborative Group, 2009,) [4].

Negative symptoms in schizophrenia include social withdrawal, emotional withdrawal, poor rapport, impairment in ability to communicate and blunted affect. Psychological side effects can be caused indirectly through other changes caused by antipsychotic use. Eosinophilia was observed in a patient with schizophrenia following the discontinuation of risperidone. (Giourou et al., 2022,) [5] This abnormal increase in eosinophils could be indicative of immune dysregulation triggered by changes in the patient's medication regimen.

Immune dysregulation can cause worsening of psychiatric conditions like depression, anxiety, schizophrenia. Obsessive-compulsive symptoms (OCS) in schizophrenia are reported to have a significant prevalence. They are considered to be rather common among individuals with schizophrenia. And antipsychotic usage has some sort of significance in management and exacerbation of OCS. They might develop through some certain types of antipsychotics, such as antipsychotics with a high antagonist activity of 5-HT_{2A}. A study reported that patients did not exhibit significant OCS symptoms before starting treatment with atypical antipsychotics. However, after treatment, there was a notable increase in YBOCS scores, indicating the development of obsessive-compulsive symptoms. (Niknafs A, 2022,) [6]

the emergence of OCS as a side effect of atypical antipsychotics necessitates careful monitoring and evaluation of patients undergoing treatment. If OCS is linked to a specific antipsychotic, clinicians may need to consider adjusting the treatment regimen, potentially by reducing the dosage or switching to a different medication.

In contrast to prior reports noting clozapine as the antipsychotic most commonly associated with de novo or exacerbated OCD/OCS, this pharmacovigilance study found aripiprazole was most frequently reported for this adverse effect. (Bradley G burk et al., 2023,) [7] In the paper it was mentioned that Patients with comorbid psychiatric conditions (e.g., schizophrenia, depression) may have pre-existing imbalances in neurotransmitter systems, which can be exacerbated by antipsychotic treatment. Individuals with schizophrenia often exhibit pre-existing neurotransmitter imbalances. This can lead to a higher risk of developing OCD/OCS symptoms. If an antipsychotic increases serotonergic activity (via 5-HT_{1A} receptor activation) while simultaneously blocking dopamine receptors, it may lead to an increase in anxiety or compulsive behaviors, manifesting as OCD/OCS symptoms.

In the (Obioha Ukaegbu et al., 2016,) [8] three cases of patients with schizophrenia were analysed. In case 1 the subject was even though successfully treated with risperidone, developed OCS 2 years ago. His OCS induced a fear of contamination and a need to carry out rituals.

In case 2 the subject was suffering with paranoid schizophrenia. She was prescribed clozapine and after

some time passed she showed improvement. However after a year she developed OCS.

She eventually restarted aripiprazol but again after a month started showing worsening of symptoms. Finally citalopram was introduced which showed overall improvement. In her case a lot of switching of prescribed antipsychotics which could be a potential reason for inconsistent re-emerging of her symptoms. As time passes our brain gets used to certain medications and might show certain side effects and dysregulations after sudden change in antipsychotics. Similarly in case 3, OCS appeared in the subject after being on clozapine for several years. He started fluoxetine and after a month no improvement was reported. After two months passed his symptoms started worsening. Eventually fluoxetine's dose was increased. In this case too there is a gradual shift in his antipsychotics from clozapine to fluoxetine. Switching of antipsychotics can be considered a possibility of exacerbation of obsessive compulsive symptoms. However more research is required to say so. It's not quite uncommon that clinicians might not want to switch the current antipsychotics or even the current dosage of prescribed medicines. In (Kaitlyn Morgan & Leah Rickert, 2022,) [9] "The majority of patients were continued or restarted on previous antipsychotic medications or had doses titrated within FDA-recommended doses. Continuation of previous antipsychotic during an acute exacerbation of schizophrenia symptoms could indicate a lack of medication adherence in the outpatient setting contributing to a large number of the admissions in this study population." Which might suggest that patients find it troublesome to adhere to the antipsychotic medication leading to exacerbation.

Majority of the patients were continued or titrated to the same medication. This may have done so cause clinicians might be scared of the adverse effects with switching antipsychotics such as exacerbation of symptoms. Withdrawal symptoms appear to occur frequently after abrupt discontinuation (Johnny Su et al., 2012,) [10]. Withdrawal effects may arise when the body responds adversely to a rapid reduction in medication. They may occur if effects occur due to the body's physiological and biochemical adaptations to a substance, such as a medication or drug, over time. When a person regularly uses a substance, the body adjusts to its presence, leading to changes in neurotransmitter levels, receptor sensitivity, and overall homeostasis. The body may develop a physical dependence on a substance, meaning that it relies on the substance to function normally. When the substance is removed, the body struggles to maintain its equilibrium, leading to withdrawal symptoms. Which further introduces OCS as a potential withdrawal symptom of schizophrenia and removal of current antipsychotic as a cause of its exacerbation.

Another factor which affects different conditions regarding antipsychotics is dosage regulation. Either increase or decrease can of prescribed antipsychotic dose can further draft many conclusions about various side effects, exacerbation or withdrawal. When not shown proper improvement over time, clinicians might increase the dosage to observe improvement. However In (Myrto T Samara et al., 2018) [11] the review found no clear evidence that increasing the dose of antipsychotics leads to better outcomes compared to maintaining the current dose. Exacerbation of psychotic symptoms on antipsychotic reduction may not represent evidence for the need of a higher dose of antipsychotic (Mark A Horowitz & Joanna Moncrieff, 2024,) [12]. The onset of psychotic symptoms is more significantly affected by the speed of dose reduction than by merely achieving a lower dose. A rapid decrease in antipsychotic medication can create an imbalance between neurotransmitter levels and receptor sensitivity. This imbalance may lead to increased dopamine activity, which can trigger withdrawal or psychotic symptoms. To reduce the risk of these symptoms, a gradual tapering of the medication is advised. These symptoms may not signify a resurgence of the underlying disorder but rather a response to the sudden alteration in medication. Antipsychotics primarily work by blocking dopamine receptors. Higher doses can lead to more significant receptor

blockade, which may exacerbate side effects related to dopamine deficiency, such as akathisia (restlessness) or parkinsonism (tremors, stiffness).

Depressive symptoms can also be affected by antipsychotic use. Depressive symptoms refer to a range of emotional, cognitive, and physical manifestations associated with depression. These symptoms can vary in intensity and duration and may significantly impact an individual's daily functioning and quality of life. In (Del D Miller et al., 1994,) [13] The study found that negative symptoms increased after the discontinuation of antipsychotic medication. These symptoms may include lack of motivation, loss of interest, pleasure, disorganized thinking etc. It was also shown that overall depression score also increased with increase in negative symptoms. Not only discontinuation increased negative symptoms but also depressive symptom.

Depressive symptoms themselves have their own effects on overall mental being. In (Lindsay A Bornheimer & James Jaccard, n.d.,) [14] Findings indicated that symptoms of depression and positive symptoms of psychosis (i.e., hallucinations and delusions) independently predicted suicidal ideation, supporting the hypothesis that hallucinations, delusions, and symptoms of depression would independently predict suicidal ideation. Basically suggesting the strong correlation between the three. Therefore depressive symptoms also effect suicide ideation and positive symptoms. The clinical study by (Marco Innamorati et al., n.d.,) [15] indicates that, upon examining the study, there was no statistically significant change in their depressive symptoms following treatment with atypical antipsychotics.

Which further leads to the co relation between depressive symptoms suicidal thoughts and positive symptoms of psychosis.

Antipsychotics can certainly have varied effects. These effects can be managed by introducing proper planning in prescribing antipsychotics and having a more thorough examination of varied symptoms and changes caused. In past few methods have shown positive effects by causing certain changes in antipsychotic prescribing and management.

One method being tapering. Various tapering schedules can be implemented in the treatment depending on the patient. The findings in (G De Kuijper et al., n.d.,) [16] suggest that clinicians can safely taper off antipsychotics prescribed for behavioral symptoms without worrying about degradation in patient behavior. It supports the idea that gradual dose reduction can lead to improved outcome. Although this isn't specifically true for schizophrenia but still shows the benefits of tapering antipsychotics and can be considered a potential method. Another method being combining two antipsychotics which gradually decreases the dose of one antipsychotic.

It is common practice to prescribe a combination of atypical and conventional antipsychotic. (W J Broekema et al., 2007,) [17] potential increase in dosage of a single medication can cause side effects so combining it with another medication can reduce the individual dosage and prevent these adverse effects. This method of combining antipsychotics is shown to be beneficial. For instance in (A Aissa et al., 2021,) [18] aripiprazole (20mg) and clozapine which was tapered down to 150mg) was given in a combination. Using both medications together may allow for a reduction in the dosage of clozapine while still effectively managing the patient's symptoms. This approach can be beneficial in minimizing potential side effects associated with higher doses of clozapine, while still providing adequate symptom control through the addition of aripiprazole. However more evidence is required to indicate benefits of combining antipsychotics as a beneficial method.

Conclusion

Antipsychotics help in reducing the negative and positive symptoms related. However if not managed accordingly can have varied effects on the patients. These effects can vary and affect both mental and physical well being. Similar antipsychotics can have various side effects. One such being increase in negative symptoms including social withdrawal, emotional withdrawal etc. further it is seen that immune dysregulation is also a side effect caused by antipsychotics. One such being eosinophilia. Depressive symptoms can also be affected. In some cases antipsychotics might not show any improvement in depressive symptoms or even worsen the depressive symptoms. Identifying the depressive symptoms will further help in prescribing antipsychotics accordingly and introducing newer strategies in overall treatment. Obsessive compulsive symptoms are also discussed as being a major antipsychotic symptom. Which shows the varied types of ways antipsychotics can affect our health either it be our immune system or physical movements. Identifying other sources other than general symptoms can help find potential threats. Antipsychotic prescribing is the major factor determining of potential withdrawal exacerbation or side effects caused. Determining the time intervals of prescribing antipsychotics is important. After being on the same antipsychotics our brain processes gets adjusted accordingly on a neurobiological level. Abruptly switching to another antipsychotic can worsen the symptoms leading to a potential relapse. Abruptly switching can also cause withdrawal symptoms. The dose prescribed is also to be considered an important factor as high dosages can be sometimes causing harmful effects. Introducing potential strategies in the treatment plan can help prevent these effects. One such being combining two antipsychotics which helps by gradually decreasing the dosage of a specific antipsychotic which might be causing any harm while still maintaining the equilibrium. Another such method being gradually tapering antipsychotics. Slowly Decreasing the antipsychotic dosage and transitioning to a newer antipsychotic can prevent the abrupt change and allows our brain to process the overall neurobiological changes going on. Overall more evidence is required to prove the benefits of these methods in antipsychotic treatment.

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