

Recent management of extrapyramidal syndrome in antipsychotic use

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ABSTRACT

Antipsychotic drugs are crucial for treating mental illnesses but can cause various side effects due to their non-selectivity and high affinity. A study has shown that the prevalence of extrapyramidal side effects among patients with schizophrenia spectrum disorder on antipsychotic medication was 42.6%, with specific side effects including tardive dyskinesia, parkinsonism, and akathisia. These symptoms can significantly impact individuals' quality of life, so effective management is crucial to minimize their impact. Recent advances in the management of EPS include the use of atypical/second-generation antipsychotics and anticholinergic medications. These have been shown to be effective in managing EPS and have a better safety profile than first-generation antipsychotics. Other important strategies for managing EPS include using lower doses of antipsychotics, combination therapy, anticholinergic drugs, and non-pharmacological interventions such as physical therapy, lifestyle modifications, and addressing potential non-adherence to treatment.

Keywords: antipsychotic, extrapyramidal syndrome

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INTRODUCTION

Antipsychotics have crucial role for treating schizophrenia, depression and other mental illness. It targets the D2 receptor and has different chemical structures. Antipsychotic drugs have low selectivity to the target site and can cause various side effects due to their non-selectivity and high affinity. It includes extrapyramidal disturbance, hyperprolactinemia, and cognitive decline (Orzelska-Górka et al., 2022).

A large study of antipsychotics taken by US women has confirmed the increased risk of breast cancer associated with the use of antipsychotic drugs that elevate prolactin, as found in other recent observational studies (Rahman et al., 2022). Another study also found significant associations between non-alcoholic fatty liver disease (NAFLD) and body mass index, as well as the total dose of antipsychotic drugs that carry a risk of metabolic syndrome and hyperprolactinemia. (Koreki et al., 2021). Typical antipsychotics can increase deficit symptoms by blocking DA receptors in the nigrostriatal pathway. They can also cause sedation through histamine receptor blockade and cardiovascular disorders through α_1 adrenergic receptor antagonism. (Orzelska-Górka et al., 2022).

The second generation of antipsychotics including clozapine and risperidone, not only block D2 receptors but also show antagonism towards 5HT_{2A} receptors. It leads to a partial reduction of negative symptoms. Antagonizing 5-HT_{2A} receptors can produce antipsychotic effects by reducing dopaminergic transmission in the mesolimbic pathway, which is caused by a decrease in glutamate release in the VTA. Atypical antipsychotics have fewer side effects due to lower affinity for D2 receptors or a preference for mesolimbic over nigrostriatal pathway receptors which can lower the extrapyramidal incidence but they may cause weight gain in patients (Orzelska-Górka et al., 2022).

A study has shown that among patients with schizophrenia spectrum disorder on antipsychotic medication, the prevalence of extrapyramidal side effects was 42.6%. The specific side effects and their prevalence rates were tardive dyskinesia (7.9%), parkinsonism (38.6%), and akathisia (3.6%). Tardive dyskinesia was associated with elderly patients, while the duration and severity of illness and type of illness were associated with parkinsonism. (Shettima et al., 2023) It is important to be wisely selective using antipsychotics in clinical applications related to extrapyramidal syndrome.

DEFINITION

Extrapyramidal side effects (EPS), also known as drug-induced movement disorders, are among the most common side effects experienced by patients taking dopamine receptor blocking agents (antipsychotics). These side effects include dystonia, akathisia, and parkinsonism, which can occur more acutely, as well as more chronic manifestations of tardive akathisia and tardive dyskinesia.

Types of extrapyramidal symptoms:

1. Acute dystonia usually presents as severe muscle spasms, particularly in the neck, eye, tongue/jaw.
2. Akathisia is characterized by an inner restlessness and an inability to sit still (motor restlessness).
3. Parkinsonism is a movement disorder that causes resting tremor, cogwheel rigidity, postural instability and bradykinesia.
4. Tardive dyskinesia is a chronic movement disorder characterized by abnormal asymmetric involuntary movements, particularly in the facial area, tongue and/or limbs. (D'Souza and Hooten, 2023).

EPIDEMIOLOGY

A systematic review and meta-analysis found that the pooled prevalence of antipsychotic-induced extrapyramidal side effects (EPSEs) was 37%, with parkinsonism, akathisia, and tardive dyskinesia occurring at rates of 20%, 11%, and 7%, respectively. Egger's regression test confirmed publication bias in studies reporting akathisia and tardive dyskinesia. (Ali et al., 2021) In a study of 11,642 schizophrenia patients prescribed atypical antipsychotics, 21.2% experienced extrapyramidal side-effects (EPS) within the first year. (Kadakia et al., 2022).

ETIOLOGY

A meta-analysis of 110 studies with 382 dose arms found that almost all antipsychotics were associated with dose-dependent extrapyramidal symptoms (EPS), with varying degrees of risk. Quetiapine and sertindole had negligible risks across all doses, while cariprazine, iloperidone, and zotepine had very low-quality data. The risk of EPS increased substantially when D2R occupancy exceeded 75-85%, except for D2R partial agonists that had smaller odds ratios despite high D2R occupancies. (Siafis et al., 2023). Centrally acting dopamine receptor blocking agents, namely the first-generation antipsychotic haloperidol and the neuroleptic phenothiazine, are the most common drugs associated with EPS. While EPS is less common with atypical antipsychotics, the risk of EPS increases with increasing doses. Other agents that block central dopaminergic receptors have also been identified as causes of EPS, including antiemetics (metoclopramide, droperidol, and prochlorperazine), lithium, serotonin reuptake inhibitors (SSRIs), stimulants, and tricyclic antidepressants (TCAs). In rare situations, antivirals, antiarrhythmics, and valproic acid are also involved. (Krutika Chokhawala and Lee Stevens, 2023).

Typical antipsychotics are the classic standard drugs and often cause severe EPS. Based on their chemical structure, they are grouped into several classes, namely phenothiazines (e.g. chlorpromazine and flufenazine), butyrophenones (e.g. haloperidol), benzamides (e.g. sulpiride and tiapride), and others. On the other hand, atypical antipsychotics were developed as the second generation, and are generally less potent than typical ones in inducing EPS. These include Serotonin Dopamine Antagonist (SDA) with strong blocking action for 5-HT₂ receptors, Multi-Acting-Receptor-Targeted-Antipsychotic (MARTA) and dopamine D₂ partial agonists. In addition to reducing EPS, these drugs were initially expected to be superior to typical antipsychotics in terms of their efficacy for treating negative symptoms (e.g. apathy and emotional withdrawal). (Krutika Chokhawala and Lee Stevens, 2023).

PATOPHYSIOLOGY

Dopaminergic neurons have four main pathways in the central nervous system: mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular. Antipsychotic drugs, particularly conventional ones, have a higher affinity for binding with dopamine receptors in all pathways. Blockade of dopamine receptors in the mesolimbic and mesocortical pathways is responsible for treating positive symptoms and worsening negative symptoms, while blockade in the deep striatum is responsible for antipsychotic-induced extrapyramidal side effects. EPS symptoms may be difficult to distinguish from other movement disorders, and up to one-third of new-onset schizophrenia patients who have never been treated may present with signs. (Suski and Stacy, 2023)

MANAGEMENT

Reduce the dose of antipsychotics or give anticholinergic drugs might be needed to manage side effect such as extrapyramidal syndrome (EPS). If symptoms persist, discontinue the medication and replace with a second-generation antipsychotic, especially clozapine. (Kemenkes RI, 2015) Acute onset of EPS may require emergency airway intervention. Physical medicine and rehabilitation consultations can provide useful treatment modalities for reducing dystonia, including relaxation training, biofeedback, and electrical nerve stimulation. For the treatment of akathisia, strategies similar to managing dystonia are used, and additional therapeutic strategies include the administration of betaamantadine, clonidine, blockers, benzodiazepines, and antidepressants. (Cho and Hallett, 2016).

Tardive dyskinesia can be treated by discontinuing or reducing the dose of the causative drug, switching to atypical antipsychotics, and trying various medications such as benzodiazepines, amantadine, and tetrabenazine. Levetiracetam, zonisamide, pregabalin, vitamin B6, and vitamin E have also been reported as therapeutic. Drug-induced parkinsonism is treated by discontinuing or reducing the dose of the causative drug, switching to atypical antipsychotics, and administering drugs used for Parkinson's disease. Prophylactic administration of anticholinergic drugs to prevent or reduce EPS has been studied, but is generally not recommended due to bothersome side effects. First-generation antipsychotics are used less frequently nowadays. Second-generation atypical antipsychotics can cause EPS, although at a lower rate. (Waln and Jankovic, 2013).

RECENT MANAGEMENT

The latest management guidelines recommend reducing the dose of antipsychotics and using anticholinergic drugs such as trihexylphenidil or diphenhydramine for dystonia, akathisia, and parkinsonism. For tardive dyskinesia, lower the dose of antipsychotics or switch to a second-generation antipsychotic like clozapine if symptoms persist or worsen. (Kemenkes RI, 2015).

A. Changing Antipsychotic Medications

Switching from FGAs to SGAs is one of the most effective ways to manage EPS. SGAs have a lower incidence of EPS than FGAs due to their weaker affinity for dopamine D2 receptors and their antagonistic effect on serotonin 5-HT_{2A} receptors. SGAs such as clozapine, quetiapine, and olanzapine have been shown to be effective in treating symptoms of EPS, including tardive dyskinesia. Patient's medical history, comorbidities, and drug side effects when switching antipsychotics are needed to manage it. For example, clozapine has a risk of agranulocytosis, and olanzapine can cause weight gain and metabolic syndrome. Studies have shown that SGA has greater affinity for dopamine D2 receptors in the mesolimbic pathway than the nigrostriatal pathway, which reduces the risk of EPS. SGA also has lower affinity for histamine H1 receptors and muscarinic M1 receptors, which reduces the risk of sedation and anticholinergic side effects. Therefore, SGAs are favoured over FGAs in the management of patients with EPS. (Stroup and Gray, 2018).

B. Use of Atypical Antipsychotic Drugs

Atypical antipsychotic drugs are a newer class of drugs that have been shown to be effective in treating EPS. These medications have a lower incidence of EPS compared to FGAs and are

less likely to cause tardive dyskinesia. They work by blocking dopamine D2 and serotonin 5-HT_{2A} receptors, which may reduce the risk of EPS.

Examples of atypical antipsychotic medications include olanzapine, risperidone, and aripiprazole. (Stroup and Gray, 2018)

Newest studies have found some medications that can help to reduce extrapyramidal syndrome in antipsychotic use:

1. Aripiprazole is a dopamine stabilizer that acts as a partial agonist towards the D₂ receptor. It can block dopamine receptors in the mesolimbic pathway at high concentrations and can have antipsychotic effect and stimulate them in the prefrontal cortex at low concentrations. This intrinsic activity may explain its clinical effectiveness and favourable safety profile. Unlike conventional antipsychotics, aripiprazole can work as a functional antagonist and agonist in areas of overactivity and underactivity, respectively. It is effective for patients with schizophrenia who have increased activity of mesolimbic dopaminergic neurons and decreased mesocortical activity. (Pahwa et al., 2021)
2. Brexpiprazole is a new atypical neuroleptic that exhibits partial agonism to D₂/D₃ and 5HT_{1A} receptors, antagonism to 5HT_{2A} and α -1B/2C receptors, and has low affinity for H₁ receptors. It has potential to cause fewer side effects than aripiprazole due to its lower intrinsic activity to the D₂ receptor and increased potency of antagonism towards 5HT_{2A} receptors. (Ślifirski et al., 2021) Brexpiprazole demonstrated efficacy in treating acute exacerbations and in maintenance treatment for adults diagnosed with schizophrenia, with a good safety and tolerability profile. (Kikuchi et al., 2021)
3. The D₃ receptor is a potential target for new atypical neuroleptics, playing a role in the regulation of the reward system, emotion, motivation, and attention. Cariprazine, a partial agonist at the dopamine D₂ and D₃ and the serotonin 5HT_{1A} receptors, has been approved for the treatment of schizophrenia and bipolar disorder, demonstrating efficacy without significant weight gain or metabolic effects, but with a higher incidence of akathisia compared to other drugs. (Hope and Keks, 2022)
4. Lurasidone is an atypical antipsychotic drug used for treating schizophrenia and depressive symptoms in bipolar disorder. It is a full antagonist of D₂, 5HT_{2A}, and 5HT₇ receptors, and a partial agonist of 5HT_{1A} receptors, with the antipsychotic effect likely due to D₂ receptor blockade and strong antagonism to 5HT₇ receptors. Lurasidone has no significant impact on metabolic parameters or weight gain and may be a suitable treatment option for selected patient groups. (Ślifirski et al., 2021)
5. Asenapine, a receptor-targeted multi-acting antipsychotic, is approved for the treatment of schizophrenia and BD in adults and paediatric populations. It has a low risk of anticholinergic side effects and is administered sublingually or transdermally. Asenapine is safe for patients with renal or mild to moderate liver failure and has been shown to be effective in clinical trials and paediatric populations. (Musselman et al., 2021)
6. Lumateperone (ITI-007) is a new antipsychotic medication approved by the FDA for the treatment of schizophrenia in adults. It works through multiple systems and may target depressive and negative symptoms as well as cognition. Lumateperone achieves maximal antipsychotic effect at only 39% receptor occupancy, has a therapeutic window, and significantly fewer adverse effects compared to other antipsychotics. (Ślifirski et al., 2021).
7. Pimavanserin is an inverse agonist of the serotonin 5HT_{2A} receptor and is approved for treating hallucinations and delusions in Parkinson's disease patients. Unlike other

antipsychotic drugs, it does not bind to dopamine D2 receptors, making it an ideal pharmacotherapy for Parkinson's disease psychosis without exacerbating motor symptoms. It is also a promising drug for dementia-related psychosis. (Ślifirski et al., 2021).

8. Risperidone ISM had a lower incidence of extrapyramidal symptoms (EPS) than Paliperidone palmitate (PP), but the difference was not statistically significant. However, Risperidone ISM had a significantly lower incidence of EPS and use of anticholinergic agents compared to Aripiprazole monohydrate once-monthly (AOM), suggesting a superior tolerability profile for clinically relevant EPS. The study concludes that Risperidone ISM has a favorable safety and tolerability profile compared to other antipsychotic therapies for treating patients with schizophrenia in the maintenance setting. (Sánchez et al., 2023).

B. Lower doses of antipsychotics

Another promising approach to managing EPS is the use of lower doses of antipsychotics. Studies have shown that lower doses can be as effective as higher doses in treating symptoms of psychosis, while reducing the risk of EPS. This approach is particularly useful for patients who are at higher risk of developing EPS, such as elderly patients or those with a history of EPS. By using lower doses, healthcare providers can not only treat the symptoms of psychosis but also reduce the risk of EPS. (Kemenkes RI, 2015)

Combination therapy has also emerged as an promising approach to managing EPS. This therapy involves using multiple medications to target different aspects of EPS. For example, a patient may be prescribed antipsychotic medications to treat their psychotic symptoms, along with medications that target the specific EPS symptoms they are experiencing. This approach can be very effective in reducing EPS symptoms while treating the underlying condition. (Kemenkes RI, 2015)

C. Use of Anticholinergic Drugs

Anticholinergic drugs such as benztropine and trihexyphenidil have been used to treat EPS by blocking the action of acetylcholine in the basal ganglia, which can reduce dystonia, rigidity and tremor. However, anticholinergic drugs may cause side effects such as dry mouth, blurred vision, constipation, and cognitive impairment, especially in elderly patients. Weigh the benefits and risks of using anticholinergic drugs is needed in managing EPS and consider using them as adjunctive drugs rather than first-line treatment. (D'Souza et al., 2018).

D. Non-pharmacological interventions

Non-pharmacological interventions such as physical therapy, occupational therapy, and speech therapy have been shown to be effective in managing EPS in antipsychotic use. These interventions focus on improving the patient's motor function, coordination and balance. Physical therapy has been shown to be particularly effective in treating tardive dyskinesia, which is a type of EPS characterised by involuntary movements of the face and limbs. Occupational therapy and speech therapy have been shown to be effective in treating dysphagia, which is a common side effect of antipsychotic use. (Cornett et al., 2017).

Physical therapy can help improve range of motion, strength, balance and gait in patients with dystonia or akathisia. Exercise can reduce the severity of akathisia and tardive dyskinesia by increasing dopamine release and improving blood flow to the brain. Biofeedback techniques such as electromyography (EMG) and electroencephalography (EEG) can help patients gain control over their involuntary movements by providing real-time feedback on muscle activity and brain waves. In addition to pharmacological and non-pharmacological interventions, lifestyle modifications can also play a role in managing EPS. (Salem et al., 2017).

Regular exercise, a balanced diet, and adequate sleep can help to reduce the severity of symptoms and improve overall health outcomes. Encourage to engage in activities that improve physical and mental health, such as yoga, meditation, or other relaxation techniques. It is also important to monitor patients regularly for potential side effects of antipsychotic medications, such as metabolic syndrome and cardiovascular disease. The clinician should work closely with the patient to develop an individualised treatment plan that takes into account their medical history and risk factors, and adjust treatment as needed to optimise outcomes. (Siafis et al., 2017).

Another important aspect of managing EPS is addressing potential non-adherence to treatment, which can be a significant barrier to effective treatment. Patients may be hesitant to take antipsychotic medications due to concerns about side effects or the stigma associated with mental illness. It can help address this issue by educating patients about the benefits and risks of medication, as well as providing support and resources to help patients manage any side effects they may experience. Address the emotional and psychological impact of the disorder on patients and their families might be needed. (Stroup and Gray, 2018).

Patients with EPS may experience a range of emotional and psychological symptoms, such as anxiety, depression and social isolation. Psychotherapy and other forms of counselling can be effective in helping patients overcome these symptoms and improve their quality of life. Overall, the management of EPS requires a comprehensive and individualised approach that can address the complex challenges associated with antipsychotic use. By keeping up with the latest developments in treatment options and working collaboratively with patients and their families, healthcare providers can help improve the quality of life of patients with EPS and promote better health outcomes overall. (Pringsheim and Barnes, 2018).

PROGNOSIS

Extrapyramidal symptoms (EPS) can resolve spontaneously or with medication, but tardive dystonia, tardive akathisia, and tardive dyskinesia can persist for years with low rates of remission. A study of patients with schizophrenia reported a high cumulative persistence rate of tardive dyskinesia. (Waln and Jankovic, 2013).

COMPLICATION

Antipsychotic and metoclopramide-induced laryngeal dystonia is more common in young men. Rhabdomyolysis is a rare complication of drug-induced dystonia, while dystonic storms are triggered by infection and medication adjustment. Failure to diagnose and treat extrapyramidal symptoms (EPS) in schizophrenic patients can lead to poor adherence to medication, relapse, hospitalization, suicidal ideation, aggression, and violence. (Termsarasab and Frucht, 2017).

CONCLUSION

The management of EPS in the use of antipsychotics has seen significant progress in recent years. Newer antipsychotic drugs, lower doses, and combination therapy have been shown to be highly effective in reducing the incidence and severity of EPS. The use of SGAs is favoured over FGAs due to their lower risk of causing EPS. The use of anticholinergic drugs should be limited to patients with severe EPS or patients who do not respond to other interventions. Non-pharmacological interventions such as physical therapy, occupational therapy and speech therapy should be considered in the management of EPS. By adopting these recent developments, clinicians can improve the quality of life of patients taking antipsychotic medications.

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