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Drug Induced Parkinsonism in Schizophrenic Patient: A review article

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ABSTRACT:

Drug-induced parkinsonism (DIP) is a common parkinsonian condition that develops because of using medication to treat psychosis. After Parkinson's disease (PD), DIP is the second most common cause of parkinsonism in the elderly. It was initially identified as an adverse reaction to antipsychotics, but it is now known to occur often with antidepressants, calcium channel antagonists, gastrointestinal prokinetics, antiepileptic medications, and many other substances. Due to the clinical similarities between PD and DIP, many individuals with DIP may receive the wrong diagnosis. clinical manifestations of DIP is symmetrical, bilateral parkinsonism without resting tremor. However, because over half of DIP patients show asymmetrical parkinsonism and tremor at rest, it can be difficult to differentiate DIP from PD. The pathophysiology of DIP correlates to drug-induced changes in the basal ganglia motor pathway caused by blockade of dopaminergic receptors. Presynaptic dopaminergic neurons in the striatum are expected to be unaffected by these effects since they are restricted to postsynaptic dopaminergic receptors. Dopaminergic receptor blockers should be prescribed with caution, and physicians should keep attention on their patients' neurological symptoms, especially for parkinsonism and other movement disorders, since DIP may have a significant and lasting impact on their daily lives.

1. Introduction

Parkinsonism is a clinical condition characterized by bradykinesia, stiffness, and tremors. Parkinson's disease (PD) is the most frequent cause of parkinsonism, followed by drug-induced parkinsonism (DIP) as the second most frequent cause. [1]–[3]. Typical and atypical antipsychotics, antiepileptic drugs, and calcium channel blockers may all cause DIP. [3]. Approximately 80% of patients receiving therapy with typical antipsychotics such haloperidol, promazine, chlorpromazine, perphenazine, pimozide, and fluphenazine have evidence that these medications have been associated to several extrapyramidal symptoms. [4] Atypical antipsychotics such as risperidone, clozapine, quetiapine, olanzapine, and aripiprazole are associated with a lower rate of DIP.[5]

The following characteristics increase the risk of developing drug-induced parkinsonism: advanced age, female gender, dosage and duration of therapy, substance type, cognitive impairment, acquired immunodeficiency syndrome (AIDS), tardive dyskinesia (TD), and pre-existing extrapyramidal disease. [6] The most prominent risk factor for DIP is age [6]–[8]since dopamine concentrations decrease and nigral cells degenerate with age.[9] Another risk factor is female gender, which suggests that estrogen inhibits the production of dopamine receptors. [10]The exact mechanism carrying the gender difference in DIP has not yet been identified. Genome-wide analysis revealed the GABA receptor signalling pathway's related genes have been linked in neuroleptic-induced TD in schizophrenic patients,[11] indicating that DIP and TD are both influenced by genetic factors.

Patients with DIP are commonly misdiagnosed with PD because the clinical symptoms of DIP and PD are so similar. [12],[13] These patients are frequently prescribed antiparkinsonian drugs unnecessarily for long periods of time, even though recovery is attainable just by stopping the harmful drugs, these individuals are frequently provided antiparkinsonian treatments needlessly for lengthy periods of time. Dopamine transporter (DAT) imaging can be used to differentiate

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between distinct parkinsonism etiologies, including DIP.[14], [15]

2. Epidemiology & Etiology of Drug-Induced Parkinsonism

The precise prevalence and incidence of Drug-Induced Parkinsonism (DIP) are not well-established due to its frequent misdiagnosis as Parkinson's disease (PD). In community-based and population-based studies, the prevalence rates for DIP were reported as 2.7% and 1.7%, respectively, while PD had rates of 3.3% and 4.5%, respectively. It is important to note that 6.8% of the initially diagnosed PD patients were later reclassified as having DIP, highlighting the challenges in accurately diagnosing DIP and determining its true prevalence.[13]

Drugs can be categorized based on their relative potential to cause DIP. With well-known causal mechanisms that, in many cases, have been studied in animal models of PD, certain medications have a significant risk and are frequently related to DIP. That is how classical antipsychotics work.[16]–[24]

First-generation antipsychotics are known to be associated with a varying risk of extrapyramidal side effects (EPS), such as drug-induced parkinsonism (DIP), depending on their level of muscarinic antagonism. Drugs like zuclopenthixol or haloperidol, which have a higher degree of muscarinic antagonism, are expected to carry a higher risk of EPS compared to medications like chlorpromazine or levomepromazine, which have lower muscarinic antagonism. [25]–[29]

Clozapine is an exception, as it has the same risk of DIP as a placebo.[26] The decreased risk of drug-induced parkinsonism (DIP) associated with second-generation antipsychotics compared to first-generation neuroleptics is likely due to their differing pharmacological profiles. First-generation or typical antipsychotics, primarily work by blocking striatal D2 dopamine receptors. This blockade of D2 receptors is associated with an increased risk of movement-related side effects, such as parkinsonism. On the other hand, second-generation antipsychotics, also known as atypical antipsychotics, have a more diverse pharmacological profile. In addition to their partial agonist action on dopamine receptors, they also interact with other subtypes of receptors.[30]

Table 1: Drug associated with Drug Induced Parkinsonism [30]

Risk of DIP	Mechanism of action	Pharmacological group/drug
High	D2 receptor blockade	Typical antipsychotics (haloperidol, prochlorperazine, thioxantenes, amisulpride, flupentixol, fluphenazine, levomepromazine , pimozide promazine, sulpiride, thioridazine, zuclopenthixol) Atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole)
	Dopamine depletion	Tetrabenazine, reserpine
	Dopamine synthesis blockade	Alfametildopa
	Ca2+ channel antagonism	Flunarizine, cinnarizine
	Antiemetics	Metoclopramide, levosulpiride, clebopride
Intermediate	D2 receptor blockade (atypical)	Quetiapine, clozapine
	Ca2+ channel antagonism	Diltiazem, verapamil
	Antiepileptics	Valproate, phenytoin, levetiracetam
low	Mood stabilizers	Lithium
	Antiarrhythmics	Amiodarone, procaine

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	Immunosuppressants	Cyclosporine, tracrolimus
	Antidepressants	SSRIs: fluoxetine, sertraline MAOIs: moclobemide, phenelzine
	Antivirals	Acyclovir, vidarabine, anti-HIV
	Statins	Lovastatin
	Antifungals	Amphotericin B
	Hormones	Levothyroxine sodium, medroxyprogesterone, epinephrine (adrenaline)

3. Clinical characteristics of Drug Induced Parkinsonism

Clinically, DIP is characterized as bilateral and symmetric parkinsonism with more prominent stiffness and bradykinesia than in PD patients. Asymmetric parkinsonism and tremor are typically present in 30 to 50 percent of DIP patients; these characteristics are thought to support a PD diagnosis.[31]–[34] It's interesting to consider that DIP patients with normal tremors at rest also often show postural tremors. The identical clinical symptoms of DIP and PD suggest that people with DIP may have been in a preclinical stage of PD and that the harmful drugs might have shown their parkinsonism. Findings suggesting that in many DIP patients, parkinsonism continues or worsens after the medication has been discontinued.[32], [35]–[38] In a long-term follow-up study, parkinsonism reappeared in 7% of patients several months after it had fully resolved from DIP; in some patients, DIP may have caused PD. [32]

Table 2: Clinical characteristics of Drug Induced Parkinsonism[30]

Clinical characteristic	Drug induced parkinsonism
Age at onset	more frequently in elderly people
Symmetry of deficits	Often symmetric
Lower/upper body involvement	More severe upper part involvement less gait abnormality
Tremor	Variable
Depression	Common
Dementia	May exist prior to the onset of parkinsonism
Clinical response to dopamine agonists or L-DOPA	Poor

4. Pathophysiology of drug induced parkinsonism

The D1 family of dopamine receptors, which includes D1 and D5 receptors, and the D2 family, which includes D2, D3, and D4 receptors, are present in the brain.[39] The central dopaminergic system consists of several pathways, including the mesolimbic, mesocortical, tuberoinfundibular, and nigrostriatal pathways. Antipsychotic drugs are known to have potent D2 receptor blocking capacity, and their therapeutic effects on psychosis are related to their actions on the limbic system, where they reduce dopamine transmission. When antipsychotic drugs block D2 receptors in the striatum, this leads to the disinhibition of GABA- and encephalin-containing striatal neurons, primarily affecting the indirect pathway, while the direct pathway remains largely unaffected. This disinhibition of the indirect pathway leads to further disinhibition of the subthalamic nucleus. As a result, there is increased GABAergic inhibition of the thalamocortical projection due to facilitation of the inhibitory projection from the globus pallidus and substantia nigra pars reticulata. This pathway shares similarities with the model of the basal ganglia-motor loop disturbance seen in Parkinson's disease (PD).It has been observed that in patients with extrapyramidal symptoms (EPS) who are taking neuroleptics, more than 80% of D2 receptors are occupied by the drugs. [40]

Example of drug induced parkinsonism

- **Metoclopramide induced parkinsonism**: Metoclopramide, a dopamine-2 receptor antagonist widely used to treat various gastrointestinal disorders, can lead to, or worsen several extrapyramidal movement disorders. A study

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conducted by Miller L and colleagues focused on the significant occurrence of metoclopramide-induced movement disorders. The researchers identified and examined 16 patients who had been exposed to metoclopramide. The average age of onset for these movement disorders was 63 years, with women being affected three times more than men. Among the observed movement disorders, tardive dyskinesia was the most common. Additionally, five patients developed metoclopramide-induced parkinsonism, one patient had tardive dystonia, and another presented with akathisia. On average, patients were exposed to metoclopramide for 12 months before the onset of movement disorders. Surprisingly, even after the onset of symptoms, patients continued therapy for an average of 6 months, as the movement disorder often went unrecognized in a clinical setting and its association with metoclopramide was not identified. To prevent the persistence of disabling movement disorders, it is crucial to avoid long-term use of metoclopramide, and patients should be closely monitored for potential neurological reactions.[35]

- **Cinnarizine induced parkinsonism**: This retrospective study conducted by Marti-Masso et al. investigates the evolution of patients diagnosed with cinnarizine-induced parkinsonism (CIP) over a 15-year period. The study identified 74 cases of CIP among 172 patients with drug-induced parkinsonism (DIP). Notably, both CIP and other forms of DIP were found to be significantly more prevalent in women. However, no clinical differences were observed between CIP and other types of DIP. Most patients (66 out of 74) achieved complete recovery within 1 to 16 months after cinnarizine withdrawal. Nevertheless, 11 patients eventually developed Parkinson's disease, with four of them having previously recovered from CIP. Additionally, five patients experienced tardive dyskinesia. Their study emphasizes that CIP constitutes a substantial proportion of DIP cases referred to neurologists in regions where cinnarizine is widely prescribed. Although symptoms typically resolve following drug withdrawal, complete recovery may require more than a year. [38]
- **Calcium channel blocker induced parkinsonism**: Parkinsonism is a known potential side effect of certain calcium channel blockers (CCB). When CCB-induced parkinsonism (CCBIP) occurs, it typically improves on its own after discontinuing the offending drug. However, some patients may still experience persistent symptoms. A prospective study conducted by Garcia-Ruiz and their team examined 36 patients with CCBIP and compared their clinical and epidemiological characteristics to 38 patients with idiopathic Parkinson's disease (IPD).The study found that most patients with CCBIP experienced an improvement in symptoms after discontinuing the calcium channel blockers. Two years after CCB withdrawal, only 14% of the patients still exhibited akinetic rigid syndrome, while 92% of them still had tremors. The CCBIP group differed from the IPD group in several aspects, including age at onset, gender, presenting symptom, and history of arterial hypertension. Specifically, the patients in the CCBIP group tended to be younger at the onset of symptoms, with a higher prevalence of females. Additionally, the most common presenting symptom in the CCBIP group was tremor, and a history of arterial hypertension was more common in this group compared to the IPD group. Moreover, asymmetrical onset of symptoms was frequently observed in patients with idiopathic Parkinson's disease, but not as prevalent in the CCBIP group[33] .

5. Impact of Drug-Induced Parkinsonism in health-related quality of life in schizophrenic patients

According to the study conducted by Rekhi Gurpreet and their team, they investigated and compared the association of DIP (Drug-Induced Parkinsonism) with HRQOL (Health-Related Quality of Life) in schizophrenia. The study included 903 patients with schizophrenia, among whom 160 participants had only DIP, 119 had only TD (Tardive Dyskinesia), and 123 had both DIP and TD. The results of the study showed that HRQOL was the lowest for participants with both DIP and TD, followed by the only DIP group, the only TD group, and was the highest in the group with neither condition (neither DIP nor TD). This suggests that the

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presence of both DIP and TD had a more significant negative impact on HRQOL in schizophrenia patients compared to having only one of these conditions or none. Furthermore, the HRQOL of participants who had either only DIP or both DIP and TD was significantly lower than those who had neither condition. This indicates that the presence of DIP, with or without TD, is associated with a lower quality of life in patients with schizophrenia. [41]

6. Management of drug induced parkinsonism

The most effective therapy is to stop taking the triggering drug. So, the objective is to avoid prescribing ineffective drugs and to not have the prescription in effect for any longer than is required.[42] Atypical antipsychotics, which have a decreased risk of EPS, may be prescribed to patients who cannot stop taking antipsychotic medications due to their psychiatric illnesses, including those with schizophrenia or major depressive disorders. Dopamine antagonists should be stopped as soon as possible by patients who are taking them for simple GI disturbance, headache, dizziness, or sleeplessness. Prospective studies are required to define the mechanism of DIP, identify individual susceptibilities, determine the impact of atypical antipsychotic medications, and develop more therapy alternatives for those who are unable to stop using the offending substance.[8] After discontinuing the offending medication, DIP often disappears within a few weeks to months; however, 10–50% of individuals may experience continued or worsening parkinsonism.

Table 3: The prognosis of patients with DIP.

Type	Prognosis
1	Full and long-lasting recovery from DIP with no subsequent development of parkinsonism,
2	Persistence but not progression of parkinsonism,
3	Persistence and eventual worsening of parkinsonism,
4	Full remission of parkinsonism but later reappearance after discontinuation of the offending drug.

Only type 1 patients are considered to have "pure DIP," whereas type 3 or type 4 people may be in the preclinical stages of Parkinson's disease (PD).[43]

The treatment approach for DIP involves substituting certain drugs with a nearly similar medication that has a better side-effect profile. For instance, domperidone, which neither induces DIP nor crosses the blood-brain barrier, should be used in place of the substituted benzamides used to treat motion sickness. Additionally, when greater dosages are needed, typical antipsychotics should be used over atypical antipsychotics. The selection of an antipsychotic is a difficult decision that is influenced by several variables, including the diagnosis, the profile of possible adverse effects, any concurrent medications, and circumstances with a tendency for DIP. The medicine Parkinson's disease (PD) patients who have drug-induced psychosis respond effectively to clozapine treatment, but it may also reduce the clinical symptoms of DIP caused on by other D2 antagonists.[44]–[46]

The approach for DIP would be to closely monitor those individuals with certain risk factors for developing DIP. DIP is more common among elderly people, people who have a family history of parkinsonism, dementia, or tremor, as well as those who are taking many medications. Patients should undergo routine checks for the early indications of DIP once therapy with a possible DIP cause is initiated. Testing methods that involve quantitative assessment of certain age-averaged motor tests, such computerised tapping or walking simulations, are the most sensitive. The medication should be modified or discontinued as soon as a decrease in performance is observed.[42]

- **Pyridoxine improves drug induced parkinsonism in schizophrenic patient**

Patients with schizophrenia and severe neuroleptic-induced Parkinsonism showed remarkable and persistent improvement in movement disorders and psychotic behavior after receiving pyridoxine (vitamin B6) supplementation at a dose of 100mg per day. It is Believed that the positive effects of pyridoxine might be attributed to its potential to enhance serotonin and melatonin functions, as previous studies in rats have shown that pyridoxine deficiency leads to reduced cerebral serotonin concentrations and pineal melatonin production. Additionally, pyridoxine may also affect

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GABA and dopamine activity, although this aspect requires further investigation. Interestingly, pyridoxine has been found to mitigate levodopa-induced dyskinesias in patients with Parkinson's disease. Hence, it is suggested that supplementing with pyridoxine should be considered for psychiatric patients experiencing drug-induced movement disorders, including persistent Parkinsonism. In these situations, treating underlying pyridoxine insufficiency may help to lessen psychotic symptoms and the risk of drug-induced movement disorder.[47]

- **Anticholinergic drugs**

Anticholinergic medications such as trihexyphenidyl, benztropine, amantadine, and levodopa have been experimentally examined for their ability to relieve DIP symptoms, but this hasn't led to any definitive evidence of their effects on DIP patients.[48]–[52]High potency typical antipsychotics are frequently started concurrently with anticholinergic medications, and this practice has been demonstrated to lessen the incidence of DIP. Such conduct might be explained by the fact that elevated cholinergic activity will stimulate the basal ganglia's GABAergic inhibitory pathway. Even though WHO published a consensus statement advising against this practice in 1990. [53]

- **Smoking effect on drug induced parkinsonism in chronic schizophrenia**

Smoking has a protective effect against both DIP and idiopathic PD, which may be due to nicotine's activation of many neurotransmitters (dopamine, acetylcholine, and norepinephrine). [54] Additionally, smoking has been shown to enhance the availability of dopamine by inhibiting the enzyme monoamine oxidase-B (MAO-B).[55]According to Reuven Sandy's study, he investigated the relation between smoking and the severity of cognitive functions and the existence of drug-induced parkinsonism in a sample of 111 chronic institutionalized schizophrenia patients who were receiving neuroleptic treatment. In comparison to nonsmokers, patients who smoked had significantly less cognitive impairment and a lower prevalence of drug-induced Parkinsonism. [56]

7. Conclusion

DIP is a serious medical condition that has increased and is getting comparable to that of idiopathic Parkinson's disease. DIP was the predominant antipsychotic-induced movement disorder related to a worse HRQOL in schizophrenia patients. DIP is of significance because it generally remains unrecognized or is misinterpreted as Parkinson's disease (PD). It is a prevalent cause of parkinsonism. Furthermore, even if the offending medication is stopped, parkinsonism in DIP patients can last for an extended period and is serious enough to interfere with daily activities. The prescribing physicians must actively monitor it due to its high incidence and frequent irreversibility. Individuals with risk factors should take extra precautions and closely monitor their clinical symptoms. This study explained that the main risk factors for DIP are age, female gender, and therapy with high D2 receptor antagonistic antipsychotics. When prescribing these medications to older patients, physicians should be careful to avoid administering DRBAs and CCBs for unwarranted conditions like anxiety, sleeplessness, vertigo, or dyspepsia. They should additionally keep monitor out for neurological conditions like parkinsonism and other movement problems in these individuals. In schizophrenia, smoking may help prevent the onset of dementia and drug induced Parkinsonism. The prognosis and social abilities of schizophrenic patients may be improved by DIP early intervention and therapy. Therefore, for optimal HRQOL in patients with schizophrenia, physicians must focus on DIP prevention, identification, and effective management.

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