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A SYSTEMATIC REVIEW ON DRUG INDUCED PARKINSONISM

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ABSTRACT

Drug-induced Parkinsonism (DIP) closely resembles Parkinson's disease (PD) in motor symptoms but is caused by specific medications disrupting dopamine receptors and neurotransmitter balance. PD involves a complex interplay of genetic, environmental and biochemical factors resulting in the gradual degeneration of dopaminergic neurons. Environmental toxins and genetic mutations, such as $LRRK_2$ and SNCA, contribute to the risk of developing PD. DIP primarily occurs due to the obstruction of dopamine receptors by certain drugs, notably antipsychotics and antiemetics, affecting dopamine transmission and causing Parkinsonian symptoms. Toxin-induced Parkinsonism (TIP) arises from exposure to substances like manganese, herbicides, pesticides and specific drugs, disrupting dopaminergic pathways and altering neurotransmission. This study examines various cases of DIP, emphasizing the significance of timely identification and intervention. A thorough understanding and proactive management of DIP are crucial for alleviating symptoms and improving patient outcomes. Health care professionals need to diligently monitor patients using medications associated with DIP, adjust treatment plans and educate patients about potential side-effects. Further research is imperative to unravel the pathophysiology of DIP, considering genetic, environmental and drug-related factors, to enhance clinical practices and optimize patient care. Addressing DIP requires a multifaceted approach, including early recognition, thoughtful management and patient-centred care.

INTRODUCTION

Drug Induced Parkinsonism (DIP) is likely the most common drug-induced movement disorder and one of the most common nondegenerative causes of parkinsonism. Any medication that interferes with dopamine transmission may cause parkinsonism. The prototypical drugs are dopamine receptor blocking agents, specifically those that block D_2. DIP and Idiopathic Parkinson Disease (IPD) may be clinically indistinguishable and dopamine transporter imaging such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) can help differentiate them. The diagnosis of DIP is important to recognize, as the syndrome is reversible when the offending medication is removed.

Epidemiology: The exact prevalence of DIP is unclear because the symptoms are often under-recognized and misdiagnosed, even by neurologists.[1-5] Several large, population-based studies in Europe estimated a

prevalence of DIP ranging from 0.09 - 1.7 %.[6-12] In these same populations, IPD occurred with only a slightly higher prevalence (0.37 - 1.9 %). The percentage of patients with DIP increases with age, with the highest incidence in those between 60 and 80 years. This is likely because dopamine cells and dopamine transport decrease with age, and less dopamine receptor blockade is required to reach the threshold for parkinsonism.[13-15] Other smaller studies challenge this assertion, however.[16] Additional at-risk populations include patients with parkinsonism before antipsychotic drug exposure, especially those with subclinical PD who would eventually become symptomatic as a matter of course, but in whom the drug triggers an earlier onset. There is conflicting evidence about whether DIP is more common in males or females.[17-21]

Pathophysiology: An interruption in dopaminergic transmission underlies the pathophysiology of DIP. The most common mechanism is a structural or functional blockade of the dopamine D_2 receptor in the striatum by dopamine D_2 receptor blocking drugs. This changes the output of the indirect pathway of the basal ganglia-thalamocortical motor loop, similar to changes seen in IPD. Alteration in dopamine function can also occur with drugs like Tetrabenazine, which inhibit monoamine (including dopamine) storage into presynaptic vesicles by interfering with vesicular monoamine transporter type 2 ($VMAT_2$).[22] There are likely additional mechanisms that are not yet understood, as suggested by the wide array of medications that can cause parkinsonism without clear striatal dopamine effects.

Causative Drugs: Prototypical dopamine D_2 receptor blocking agents include not only the 1st and 2nd generation antipsychotics, but also certain antiemetic and prokinetic agents, notably Metoclopramide and Prochlorperazine. Other less commonly implicated classes of drugs include dopamine-depleting agents (Eg; Tetrabenazine), certain mood stabilizers (Eg; Na valproate), antidepressants and calcium channel blockers.

First-generation antipsychotics: DIP was 1st seen with the 1st generation (typical) antipsychotic drugs, which are potent antagonists of the dopamine D_2 receptor. Potency, route and dose of these agents all influence the risk of developing DIP. In general, the more potent the antipsychotic, the more frequently patients will develop parkinsonism.[17-23] Patients receiving intramuscular (IM) or suppository forms develop parkinsonism more quickly and at lower doses than those receiving them parenterally.[17, 24] For any given drug and formulation, higher doses lead to more D_2 receptor blockade, which increases the risk of parkinsonism.[15, 16] Across a range of drugs and potencies, parkinsonism has been reported in 32 - 50 % of older adult patients exposed to first-generation antipsychotics.[23, 25] Risk for younger patients is likely less, although exact estimates are unavailable.[17]

Second-generation antipsychotics: 2nd generation (atypical) antipsychotics are thought to cause parkinsonism less frequently than 1st generation antipsychotics because they have lower affinity for D_2 receptors and higher affinity for other targets, including serotonergic, histaminergic and muscarinic receptors.[22] However, they do have the potential to cause parkinsonism and risk is not uniform across all drugs. Among the 2nd generation antipsychotics, Lurasidone, Olanzapine, Paliperidone, Risperidone and Ziprasidone are associated with a higher risk of parkinsonism, while Quetiapine and Clozapine have a lower risk.[21, 26-28] High doses of Risperidone and Olanzapine have approximately the same risk of parkinsonism as 1st generation antipsychotic drugs.[23, 29] In clinical practice, these 2 - agents are the most likely of the 2nd generation antipsychotics to cause DIP, followed closely by Ziprasidone, Lurasidone and Paliperidone. More evidence is needed to determine the risk of DIP in newer antipsychotic drugs, including Asenapine and Iloperidone.

Aripiprazole and Brexpiprazole have a slightly different mechanism of action and

are considered "dopamine stabilizers," as they act as a D_2 receptor antagonist in dopamine-rich sites of the brain and a D_2 agonist in dopamine-poor sites.[30] While this different mechanism of action suggests that these drugs may carry a lower risk of parkinsonism, Aripiprazole was reported to cause DIP more frequently than Olanzapine in the World Health Organization (WHO) pharmacovigilance database.[21] Older adults may be more susceptible. In a 12-week randomized trial of Aripiprazole versus placebo in older adults with depression (median age 66 years), parkinsonism was reported in 17 % of patients exposed to Aripiprazole, at a median daily dose of 7 mg.[30] There has been one reported case of Brexpiprazole causing severe parkinsonism in an older woman.[31]

Pimavanserin is a newer atypical antipsychotic without affinity for D_2 receptors. It is an inverse agonist at the 5-HT_2A receptor, meaning it binds to this receptor and decreases its activity. Based on its pharmacologic profile, Pimavanserin should theoretically have no risk of DIP. It has been approved by the US Food and Drug Administration for the treatment of Parkinson disease (PD) psychosis and is an alternative to Clozapine or Quetiapine in patients with PD.[32,33]

Antiemetic and Prokinetic medications: Several commonly used antiemetics and prokinetic agents are derivatives of Benzamide or Phenothiazine antipsychotics and cause both central and peripheral blockade of dopamine D_2 receptors. These drugs,

notably Prochlorperazine and Metoclopramide, have a well-established association with a spectrum of involuntary movements, including acute dystonic reactions, DIP and tardive dyskinesia.[24, 34-36] The exact risk of DIP in patients taking these medications chronically is not known but could potentially be as high as that of 1st generation antipsychotics. Domperidone is considered to have low risk of DIP because it acts mainly on peripheral dopamine receptors;[37] however, reversible parkinsonism has been reported.[38, 39]

Dopamine-depleting agents: Tetrabenazine, Deutetrabenazine and Valbenazine cause parkinsonism through the depletion of dopamine. All three are reversible inhibitors of vesicular monoamine transporter type 2 ($VMAT_2$), which is responsible for uptake of monoamines (including dopamine) into presynaptic vesicles. Tetrabenazine is used for chorea in Huntington disease (HD) and other hyperkinetic movement disorders. In a placebo-controlled trial for HD chorea, 15 % of patients developed parkinsonism.[40] This number was consistent with another larger cohort of patients with varied hyperkinetic movement disorders.[41] Deutetrabenazine and Valbenazine are newer $VMAT_2$ inhibitors and therefore evidence is more limited. In short-term trials of Deutetrabenazine in patients with HD[42] and tardive dyskinesia[43], no worsening of parkinsonism was noted compared with placebo. Similarly, no increase in parkinsonism was reported in a trial of Valbenazine versus placebo in patients with tardive dyskinesia with up to one year of follow-up, although attrition was high in the extension study (36 %).[44, 45] However, Valbenazine-induced parkinsonism has been reported in a subsequent case series.[46] Like Tetrabenazine, these medications should be used with caution in patients who are at risk for parkinsonism until more experience is available.

Sodium (Na) Valproic acid: Na Valproic acid can cause DIP; however, this side effect is relatively rare compared with the risk of DIP with antipsychotic agents. There are more than 100 cases of Na valproic acid-induced parkinsonism reported in the literature.[47] Gamma-aminobutyric acid (GABA)-induced inhibition of dopamine transport in the basal ganglia is a suspected mechanism.

Other Drugs:

Lithium (Li): Li has been implicated in case reports to cause a parkinsonian syndrome.[39, 48-49] In a Canadian administrative database

study, patients over 65 years of age who were on Li monotherapy for a year or longer were more likely to be prescribed antiparkinsons medication than a control group of patients on monotherapy with other antidepressants, suggesting that Li by itself has the potential to produce parkinsonian symptoms.[50]

Selective serotonin reuptake inhibitors (SSRIs): Multiple SSRIs have been reported to cause de novo parkinsonism or worsen motor symptoms in patients with PD.[39] include Citalopram, Fluoxetine, Sertraline, Fl uvoxamine and Paroxetine.[51-54] However, many of the reported patients were also treated concurrently or recently with antipsychotic medications. It is not well understood why SSRIs by themselves would cause parkinsonism and the risk is likely low.

Calcium channel blockers (CCB's): Cinnarizine and Flunarizine are weak CCB's with additional antihistamine effects, serotonin receptor blockade and dopamine D_2 receptor blocking activity. They are structurally similar to Phenothiazine antipsychotics, which may explain their extrapyramidal effects. They are not approved or available in the US but are used in other regions for varied indications including treatment of vertigo, migraine prophylaxis and peripheral vascular disease. DIP caused by Cinnarizine and Flunarizine is well described in regions where these drugs are in use. The clinical presentation is similar to that in patients with antipsychotic-induced parkinsonism.[55-58] Animal studies suggest that the mechanism may be reduced dopaminergic neurotransmission, although this has not been confirmed in human studies.[59] There are a handful of case reports of other CCB's causing parkinsonism, including Amlodipine[60, 61] Diltiazem[39, 62] and Verapamil.[39, 63] This is extremely rare and because these drugs do not resemble Phenothiazines, it is not clear how they lead to parkinsonism. There is insufficient evidence to support stopping these medications prior to making the diagnosis of PD.

Others: Many other medications have been reported to cause DIP, often as single case reports.

Clinical Features: Patients with DIP present with a motor syndrome of bradykinesia, rigidity and/or resting tremor that is clinically indistinguishable from IPD. Onset of the symptoms typically occurs within a few weeks to months of the initiation of the offending agent .[69] In a large survey study published in the era of 1st generation antipsychotics, 90 % of patients who developed parkinsonism while being treated with an antipsychotic drug did so within the 1st 72 days of exposure to the medication.[17] However, parkinsonism may also occur after many years of exposure to a medication.[70, 71] In such cases, it can be difficult to exclude emerging symptoms of IPD. Rigidity is the most common finding on examination, reported to occur 65 - 100 % of the time.[17, 70, 72-75] Bradykinesia and resting tremor are more variable and found in 25 - 80 %[72, 74-75] and 35 - 88 %[17, 72-75] of patients, respectively. In clinical practice, DIP is often thought to be symmetric, but studies show that asymmetric symptoms occur 30 – 54 % of the time.[70, 74-75]

Diagnosis: DIP is a clinical diagnosis that should be considered when a patient develops motor symptoms of parkinsonism after starting or increasing the dose of an antipsychotic drug or other potentially offending agent or when a patient exhibits parkinsonism within a year of exposure to an offending drug. In the majority of cases, parkinsonian symptoms emerge over the 1st 2 - 3 months, although they may also develop years after initial exposure and take months to resolve after discontinuation.[17, 70-71] A good drug history of both current and recently discontinued medications is key to the diagnosis.

Response to drug discontinuation: DIP can be definitively diagnosed if the parkinsonism resolves within 6 - months after stopping the offending agent. Symptoms associated with DIP typically resolve after the reduction or removal of the offending agent over the course of weeks to months.[17, 71, 76] In a group

of 48 patients with DIP, it took an average of 7 - weeks for symptom resolution; 11 % of patients had symptoms persisting beyond 18 months .[72] Although prolonged DIP has been described, it is difficult to exclude an underlying neurodegenerative cause in such cases and further testing is often indicated.

Patients with ongoing drug exposure: Because DIP may be clinically indistinguishable from IPD and can even present asymmetrically with rest tremor,[77] it cannot be diagnosed by examination alone in the setting of ongoing drug exposure. Below we describe clinical clues or tests that may help to separate DIP from IPD for cases in which the offending drug cannot be stopped.

Clinical clues: The presence of concurrent movement disorders such as akathisia, orofacial dyskinesia or any other tardive syndrome suggests that parkinsonism is more likely to be caused by a medication than by PD.[40, 74, 78] By contrast, hyposmia on olfactory testing suggests the presence of an underlying neurodegenerative parkinsonism (such as IPD) as opposed to DIP.[79-81]

Ancillary testing: It is reasonable to obtain single-photon emission computed tomography (SPECT; ^{123}I-FP-CIT also known as DaTscan) in cases of suspected DIP where the causative agent cannot be stopped or when parkinsonism persists several months after stopping the drug. Other nuclear imaging modalities such as Positron Emission Tomography (PET) imaging or cardiac ^{123}I-metaiodobenzylguanidine (MIBG, iobenguane I-123) scintigraphy may distinguish DIP from an unmasked neurodegenerative process such as PD but are not widely available in clinical practice. Available evidence suggests that transcranial ultrasound of the substantia nigra does not help to differentiate DIP from IPD.[82-83]

Striatal dopamine transporter imaging: Striatal dopamine transporter imaging with SPECT (^{123}I-FP-CIT [DaTscan]) or PET (18F-FP-CIT) demonstrates reduced uptake of the radioligand in the striatum of patients with PD compared with normal uptake in patients with DIP.[78, 84-88] In a meta-analysis of 5 - studies, DaTscans had a sensitivity and specificity of 85 and 80 % in differentiating IPD from vascular parkinsonism or DIP.[82] DaTscan is widely available, while dopamine transporter PET imaging is generally restricted to tertiary care centers. Referral to neurology is generally appropriate before ordering a DaTscan, as interpretation can be difficult.

Cardiac scintigraphy: Cardiac ^{123} I-MIBG scintigraphy measures cardiac postganglionic sympathetic innervation. Cardiac uptake of MIBG is significantly reduced in PD and is normal in patients with DIP. Small studies have shown that abnormal cardiac ^{123}I-MIBG scintigraphy reliably predicts which patients will have persistent parkinsonism and response to Levodopa after drug withdrawal.[79, 82, 84] The combined use of ^{123}I-MIBG scintigraphy and DaTscan further improves predictive power.[84] However, MIBG scans for PD are not readily available for clinical use.

Patients with recurrent or irreversible symptoms: There are descriptions in the literature of DIP that resolves initially after removing the offending agent, only to recur and progress months to years later. There are also reports of patients with DIP who do not improve with removal of the offending medication, but instead continue to have worsening parkinsonism. In most cases, such irreversible or temporarily reversible symptoms are felt to represent patients with early PD pathology that is too mild to manifest motor symptoms and the dopamine receptor blockade "unmasks" their preclinical PD. This hypothesis was initially based upon the findings of autopsy studies that demonstrated Lewy body pathology in a group of patients with reversible DIP.[69, 89] Subsequent longitudinal studies using dopamine transporter imaging have also found that evidence of dopaminergic denervation on imaging is predictive of continued worsening of parkinsonism after medication discontinuation, while normal dopamine imaging correlates with full recovery.[84, 90]

Differential Diagnosis: There are numerous other causes of primary and secondary

parkinsonism. In addition to IPD, other primary neurodegenerative disorders with prominent parkinsonism include dementia with Lewy bodies, corticobasal degeneration, multiple system atrophy and progressive supranuclear palsy. Other secondary causes of parkinsonism include cerebrovascular disease, toxins, head trauma and infections.

Management: There are 2 - approaches to managing DIP: avoidance or discontinuation of known causative medications and symptomatic treatment of the parkinsonism.

Avoidance or discontinuation of causative drugs: The best way to treat DIP is to avoid using causative agents, especially in high-risk populations such as older adults. Unfortunately, this is not always possible, as some patients with psychosis need to be treated with antipsychotic agents. Mild DIP that is not bothersome to the patient does not always need to be treated, especially if the patient is otherwise stable and deriving benefit from the offending drug. If a patient develops bothersome Parkinsonism on a medication known to cause Parkinsonism, the 1st step is to stop the offending medication and follow the patient clinically to see if the parkinsonism resolves. When this is not an option, as is often the case when antipsychotics are given for severe psychiatric conditions, recommend working with the clinician prescribing the antipsychotic to determine if it is reasonable to either decrease the dose of the medication or switch to a less potent agent. For patients with IPD who have psychosis, preferred agents include Quetiapine, Clozapine or Pimavanserin if an antipsychotic is necessary.[32, 74, 91-94]

Symptomatic treatment: When the causative agent cannot be discontinued, lowered or switched to an alternative drug, symptomatic treatment of parkinsonism may be considered. Because the supporting evidence and the effectiveness of these agents are limited, clinicians should delay using them until the parkinsonism is severe enough to interfere with motor function or quality of life. Use of these therapies should be discussed with the treating psychiatrist prior to initiation. Given the limited evidence and balancing the likelihood of motor improvement versus severity of side effects and availability, we suggest trying levodopa first in most patients. If this fails to improve symptoms, other options (in order of preference) include anticholinergics, Amantadine and electroconvulsive therapy (ECT), if available.

Levodopa: Observational studies, including an open-label pilot study of Levodopa in 16 patients with disabling DIP, suggest that Levodopa provides minimal benefit.[74] However, Levodopa may improve motor symptoms in the subgroup of patients with DIP who have abnormal dopamine transporter scans and thus are more likely to have primary neurodegenerative parkinsonism. In such patients, it is even more important to stop the offending medication, if at all possible. In clinical experience, a Levodopa trial is a reasonable 1st step in treating DIP and may lessen motor symptoms, especially in patients with abnormal ancillary testing. A main concern of prescribing Levodopa to psychiatric patients is worsening of psychosis. While Levodopa tends to be well tolerated in most psychiatric patients in general, there are reports of aggravated psychosis with high doses (>1000 mg/day) and discussion with the patient's psychiatrist about the risks and benefits of Levodopa therapy should occur prior to initiation.[95-96] Practice varies and some psychiatrists advise against Levodopa in patients with psychosis. The typical starting dose of Carbidopa-Levodopa is 25/100 mg three times daily. If there is no improvement in motor symptoms, the dose can be increased gradually every couple of weeks as tolerated, up to 75/300 mg three times daily. Adverse effects and monitoring of Levodopa are reviewed separately.

Anticholinergics: Anticholinergics such as Benztropine have long been used by psychiatrists to prevent and treat extrapyramidal symptoms like parkinsonism. However, there is little high-quality evidence to suggest that they are effective.[24, 74, 97-98]

Side effects, including memory impairment, delirium and urinary retention, may be problematic, especially in older adults. Benztropine may be started at 1 - 2 mg/day in divided doses. If necessary, the dose may be increased gradually every 3 - 4 days to 6 - 8 mg/day as tolerated.

Amantadine: Amantadine has been suggested for the treatment of DIP as an alternative to anticholinergics. However, the evidence is mixed[99-100] and worsening of psychotic symptoms has been reported with Amantadine in patients with schizophrenia.[101-102] The dose of Amantadine is 100 mg 2 - 3 times daily. Livedo reticularis and ankle edema are common side effects.

Electroconvulsive therapy: There are numerous case reports of ECT improving motor symptoms in PD, with the proposed mechanism being upregulation of dopamine D_1 receptors.[103] Anecdotal evidence suggests that ECT can improve DIP as well.[103-104] ECT may therefore be an option for patients with DIP who also have a psychiatric indication for ECT, such as refractory depression.

Summary and Recommendations:

Epidemiology: DIP is one of the most common causes of parkinsonism and is often unrecognized or misdiagnosed. Older adults are at particularly high risk.

Causative drugs: Any medication that interferes with dopamine transmission may cause parkinsonism. Dopamine D_2 receptor blocking agents are the most common culprits, including 1st and 2nd generation antipsychotics, Prochlorperazine and Metoclopramide.

Clinical features: Patients with DIP present with a motor syndrome of bradykinesia, rigidity and/or resting tremor that is clinically indistinguishable from IPD.

Diagnosis: DIP should be suspected when a patient develops motor symptoms of parkinsonism after starting or increasing the dose of a medication known to cause parkinsonism or exhibits parkinsonism within a year of exposure to an offending drug. A good drug history of both current and recently discontinued medications is key to the diagnosis. DIP can be definitively diagnosed if the Parkinsonism resolves after stopping the offending agent. For patients in whom the offending agent cannot be reduced or discontinued, ancillary testing can help to identify patients with underlying primary neurodegenerative causes of Parkinsonism such as IPD.

Definitive management: Ideal treatment consists of removing the offending agent, decreasing the dose of the offending agent or switching to a less potent antipsychotic drug.

Symptomatic treatment: There are no highly effective symptomatic therapies for DIP. In patients with severe symptoms that interfere with quality of life in whom the offending medication cannot be safely discontinued, we suggest a trial of Levodopa (Grade 2C). Anticholinergics and Amantadine are also reasonable options. Electroconvulsive therapy (ECT) may be an option in patients with a concurrent indication such as refractory depression.

Conclusions: DIP is important because it is a common etiology of parkinsonism and is frequently either unrecognized or misdiagnosed as PD. In addition, parkinsonism in DIP patients is sufficiently severe to affect daily activities and may persist for long periods of time even after cessation of the offending drug. Dopamine transporter (DAT) imaging may be useful for accurately diagnosing patients with DIP and may help to identify the clinical characteristics and exact prognosis of this disorder. About 50% of patients with DIP and other movement disorders are treated with dopamine receptor blocking agents (DRBAs) for conditions unrelated to psychosis, including depression, GI disturbance, anxiety and insomnia. Physicians should avoid prescribing DRBAs and calcium channel blockers (CCBs) for inappropriate reasons such as anxiety, insomnia, dizziness or dyspepsia in elderly patients and should monitor these patients neurological signs, especially parkinsonism and other movement disorders, when prescribing these drugs.

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