Drug-induced Parkinson's disease

A clinical review

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ABSTRACT

دائماً ما تظهر أعراض تصلب العضلات والرعاش أو انعدام الاتزان بعد أخذ أدوية والأمر يرجح كون هذه الأدوية مسببه لمرض باركنسون. بالطبع تعد الإصابة بمرض باركنسون عن طريق الدواء سبب ثانوي متكرر. وتشمل الأدوية المسببة الرئيسة على مضادات الذهان، وبعض الأدوية، ومحصرات دخول قنوات الكالسيوم. الخطر المتعلق بمضادات الاكتئاب غالباً ما يعتمد على نسبة الجرعة وارتباطه بعمل الدوبامين د2. كما أن نسبة الخطر أقل في الجيل الثاني لمضادات الذهان اللا منتظم/ اللا نمطي. أما الأدوية الأخرى فمن النادر أن تظهر أعراض مصاحبة لاستخدمها وتشمل على مضادات الاكتئاب، ومضادات الفيروسات، ومضادات اضطرابات النظم، والليثيوم، وحمض الفالبرويك وغيرها. لوحظ اختفاء الأعراض في معظم الحالات بعد التوقف من استخدام الدواء لمدة 3 أشهر. كما استمرت الأعراض في حالة من عشر حالات وذلك بعد التوقف من استخدام الدواء الأمر الذي يؤدي إلى تشخيص الحالة بمرض باركسون المجهول السبب.

Drug-induced Parkinsonism must always be suspected when parkinsonian symptom like rigidity, tremor, or postural instability appear in patients receiving drug treatment. Indeed, drug-induced Parkinsonism is a frequent etiology of secondary Parkinsonism. The main causative drugs are antipsychotic, other neuroleptic drugs, and calcium-channel entry blockers. The risk associated with antipsychotics is often dose dependent and related to dopamine D2 striatal occupancy. The risk is less for the second-generation atypical antipsychotic. The other treatments rarely involved are antidepressants, antivirals, anti-arrhythmics, lithium, valproic acid, and others. Regression of symptom will be observed in most cases after a mean delay of 3 months after cessation of treatment. In one-tenth of cases, symptoms persist after drug withdrawal leading to the diagnosis of underlined idiopathic Parkinson's disease.

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Epidemiology. Drug-induced Parkinsonism (DIP) is thought to rank second in order after Parkinson disease (PD) in causing Parkinsonism, accounting for up to 20% of the PD cases.[1,2] However, it is still an under-recognized condition with significant impact on quality of life, especially in the elderly population. Unlike idiopathic Parkinsonism, DIP was noted across several studies to show clear female predominance (63%), and slightly older age of onset compared with PD.[3] In a community-based study in Brazil in an elderly population,[4] it was found that the prevalence of Parkinsonism was 7.2%, and DIP was the second most common cause (2.7%) after PD (3.3%). In a 4 year, retrospective survey in a movement disorder unit in Spain,[5] 33.8% of Parkinsonism patients fulfilled the diagnostic criteria for DIP. In that study, the ratio of DIP to PD was 1:1.83. The same results were replicated in study on Parkinsonism incidence in residents of Olmsted county in the United States of America,[6] with PD accounting for 42% of Parkinsonism followed by DIP (20%).

Medications associated with drug-induced Parkinsonism. Since its discovery in the early 1950s, a huge list of medications has been reported to cause DIP (**Table 1**).

Neuroleptics. Neuroleptics-induced Parkinsonism is the most common type of DIP. It is strongly linked with the old antipsychotics, haloperidol, chlorpromazine, and pimozide. In addition to the theory explaining

Table 1 - Potential medications reported to cause drug-induced Parkinsonism (DIP).

Potential risk	Medications
High risk	
Dopamine D2-receptor blockers	Neuroleptics; butyrophenones (haloperidol and others), phenothiazines (prochlorperazine), thioxanthenes (thiothixene), dibenzoxazepine (loxapine), others
	Atypical neuroleptics: risperidone (especially in higher concentrations)
	Anti-emetics/gastric motility agents: substituted benzamides (metoclopramide), prochlorperazine, and others)
Dopamine depleters	Tetrabenazine
Antihypertensive agents associated with DIP by reducing dopamine levels	Reserpine and alpha-methyldopa
Intermediate risk	
Calcium channel blockers with dopamine antagonist activity	Flunarizine, cinnarizine, verapamil
Certain anticonvulsants	Valproate
Mood stabilizer	Lithium (causes tremor and myoclonus)
Atypical neuroleptics	Risperidone, quetiapine, and others (especially in higher dose)
Lower risk	
Antihypertensives	Diltiazem, captopril
Antiarrhythmic	Amiodarone, procaine
Immunosuppressants	Cyclosporine, tacrolimus
Antidepressants	Fluoxetine (and other selective serotonin reuptake inhibitors), tricyclic antidepressants, and certain monoamine oxidase inhibitors, for example, phenelzine
Antifungals	Co-trimoxazole, amphotericin B
Antibiotics	Trimethoprim-sulfamethoxazole
Antivirals	Vidarabine, acyclovir (and antiretroviral drugs for HIV)
Chemotherapeutics	Thalidomide, cytarabine, ifosfamide, vincristine, tamoxifen, and cytosine arabinoside
Statins	Lovastatin and others
Hormones	Levothyroxine, medroxyprogesterone, epinephrine
Others	Bethanechol, pyridostigmine, donepezil

DIP association with neuroleptics as a consequence of D2 blockade, it was shown that the neurotoxic effect induced by neuroleptics is caused by an alteration of iron transport to the CNS, and subsequent iron deposition in the basal ganglia.[7] A recently discovered association is the occurrence of DIP even with the new atypical antipsychotics. In a large retrospective cohort study of 11,573 patients taking antipsychotics,[8] it was found that the incidence of Parkinsonism is similar in patients taking high dose atypical antipsychotic compared with the patients taking typical antipsychotic. Furthermore, patients receiving typical low-potency antipsychotics were not at increased risk of DIP compared with the atypical group.[8] In this study, olanzapine, quetiapine, and risperidone were prescribed but not clozapine. In a meta-analysis that involved a total of 2,320 participants,[9] of the new generation antipsychotic drugs, only clozapine was associated with significantly fewer extra pyramidal side effects (EPS). Of note, clozapine has higher efficacy than low-potency conventional antipsychotics. However, reduced frequency of EPS with olanzapine was of borderline significance and there was inconclusive findings related to quetiapine and risperidone.[9] It seems that small doses of typical low-potency antipsychotics; for example, chlorpromazine, have similar EPS profile compared with the high doses of the newer atypical antipsychotics, excluding clozapine. The possible mechanism related to this phenomenon is the fast-spin theory. Unlike the high potency typical antipsychotics, the new atypical medications bind transiently to D2 receptors, a condition known as "fast-off D2 theory" (**Table 2**). This transient binding is sufficient for antipsychotic effects to take place, and then allows the receptors to be available to naturally present dopamine, thus producing less EPS.[10]

Table 2 - Occupancy of brain dopamine receptors by antipsychotic drugs.

Drug	Percent occupancy		
	D2	D3	D4
Haloperidol	85	52	57
Chlorpromazine	78	62	17
Risperidone	63-89	25-61	22-55
Olanzapine	43-89	10-55	27-80
Quetiapine	51	24	88
Clozapine	38-63	62	49-73

Studies showed that clozapine despite its high D2 receptors occupancy (71%) measured 1-2 hours after drug administration, the occupancy declined to 26% after 24 hours. This is true for other atypical new antipsychotics such as quetiapine. The phenomena of transient and fast disassociation from the D2 receptors have been reported with the new antipsychotic drugs. This feature was publicized that atypical antipsychotic will exhibit their antipsychotic function and will less likely cause motor side effects.[10] It was also suggested that the favorable side effects profile of the atypical antipsychotic might be related to the dual blockade of D2 and 5-HT2A receptors.[11] Serotonin inhibits the release of dopamine in the striatum. Thus, the atypical antipsychotic blocking the serotonin will promote dopamine release and prevent EPS. On the other hand, 5-HT2A receptors are not as abundant in the limbic system as in the striatum, and apparently this is convenient for the action of antipsychotic drugs that need to decrease the dopamine level in the limbic system. However, this idea has been recently challenged by the fact that the clinical trials have compared high doses of typical antipsychotics where D2 occupancy is more than 90%, to low doses of atypical antipsychotics that give rise to less than 80% occupancy. These studies concluded that the low incidence of EPS symptoms is likely related to the dosing regimen rather than protective serotonergic role.[12]

Anti-emetics. Anti-emetics are usually overlooked as a causative agent of DIP.[13] Metoclopramide, the prototypical antiemetic, accounts for nearly a third of all drug-induced movement disorders.[14] It is commonly prescribed in the elderly. Metoclopramide-induced Parkinsonism is typically encountered within the first 3 months of metoclopramide therapy, the parkinsonian findings resolve in most patients within 2 months after drug therapy is discontinued.[15] The recovery period; however, may range from 7 days to one year.[15,16] Domperidone has long been recognized for its safe neurological profile, which is attributed to its poor penetration of the blood brain barrier, and yet, there are an increasing number of reports on the domperidone EPS profile. This might be explained by a defective blood brain barrier as is the case in the elderly, and post cerebral infarction, and post brain surgery.[17-19] Chronic treatment with clebopride is also associated with reversible Parkinsonism, and tardive dyskinesia, which is potentially irreversible.[20,21]

Calcium channels blockers. This is well described with cinnarizine and flunarizine, and these agents are used as vestibular sedatives in patients with vertigo.[22] A possible mechanism of Parkinsonism with calcium channel blockers is: D2 blockade,[23] inhibition of energy-dependent vesicular uptake of dopamine,[24] and mitochondrial damages.[25] It is of note that calcium channel blockers used in cardiac conditions have less clear association with DIP, but it has been reported.[26] It is also noteworthy that the main delay of occurrence of Parkinsonism syndrome elicited by calcium channel blockers (at least 12 months) is longer for the peripheral more than the central dopaminergic antagonism.[27]

Antiepileptics. This has been reported in several case series with valproate. The proposed pathophysiology behind DIP found with valproate is mitochondrial respiratory chain dysfunction. There is defective function of the mitochondrial enzyme Nicotinamide adenine dinucleotide (NADH), Coenzyme Q10 (CoQ), reductase (complex one) of the respiratory chain in idiopathic PD.[28] Valproate affects complex one in vitro studies.[29] Another presumed mechanism of "reversible valproate-induced Parkinsonism" is excessive GABAergic activity in the basal ganglia as seen in PD.[30] In a study of 50 patients taking valproate, 3 out of the 50 patients or 6%, were found to have DIP. These patients were not on neuroleptics or other treatment that is known to cause EPS, and were taking valproate for a minimum of one year. Furthermore, upon stopping the valproate, 2 of these patients showed marked improvement. All these 3 patients showed normal dopamine transporter scans.[31]

Clinical features (Table 3). Differentiating DIP from PD or other parkinsonian syndromes can be elusive on many occasions. However, there are certain clinical features that help in establishing the correct diagnosis, and aid commencement of the patient on the appropriate treatment. Drug-induced Parkinsonism might have acute to subacute onset with a temporal relationship to a newly started medication, occasionally within a few days. The average duration was found to be approximately 3 months.[32] Commonly, bradykinesia is the initial presentation that might be overlooked if not associated with other prominent signs like tremors, or bradykinetic-rigid presentation.[33] Freezing was shown to have a rare occurrence in DIP compared with other parkinsonian syndromes; nevertheless, other gait abnormalities are not uncommon accounting for an increased risk of falling in the elderly.[34] Unlike PD, which is often asymmetrical even at advanced stages, DIP is characterized by symmetrical signs, although asymmetrical disease is not a rare presentation.[35] Tremors mark the onset of the disease in a third of cases, and the complete triad of Parkinsonism is found only in 25% of patients with DIP. Tremor is more pronounced in action and posture, unlike idiopathic PD in which the

Table 3 - Clinical features of drug-induced Parkinsonism and Parkinson's disease.

Variables	Drug-induced Parkinsonism	Parkinsonism
Symptoms at onset	Bilateral and symmetric or asymmetric	Unilateral or asymmetric
Onset	Acute or subacute	Chronic
Course with appropriate treatment	Regressive	Progressive
Response to anticholinergic drugs	Evident	Mild to moderate
Response to levodopa	Poor	Marked
Akathisia	Present	Absent
Other associated features	Orobuccal dyskinesia and rabbit syndrome	Motor fluctuations
Incidence of rest tremor	More evident	Less evident
Gender	More in females	More in males
Freezing	Uncommon	Common

tremors are more frequent at rest.[36] Moreover, one study concluded that fine postural tremors are a common sign detected in psychiatric patients on antipsychotic medications.[37]

An important observation in DIP is akathisia, a sense of inner restlessness and feeling the urge to move. This usually develops earlier than Parkinsonism, and maybe observed within days after drug initiation and it is more common with typical more potent antipsychotics.[38,39] Other associated features that can point toward the diagnosis are tardive dyskinesia with an annualized incidence of 3.9% for second-generation antipsychotics, and 5.5% for first-generation antipsychotics.[40] Rabbit syndrome, which is a form of oral masticatory dyskinesia has been strongly associated with high potency antipsychotics such as haloperidol,[41] however, this syndrome has also been reported with newer antipsychotic drugs especially Risperidone.[42-44] As is the case in Parkinson disease, cognitive dysfunction is an observed feature in DIP that involves most cognitive domains even in patients with a negative history of cognitive disorders. Fortunately, most of the times, it is transient like the other motor symptoms.[45,46]

Risk factors associated with drug-induced Parkinsonism. 1. Neuroleptic use. This is the single most important predicting factor, increasing the risk more than 5 fold when compared with non-users.[47] It is estimated that up to 50% of neuroleptic-users will eventually develop DIP.

2. Age. Increasing age is also an important risk factor, this is presumptively related to nigrostriatal age-related degeneration.[48]

3. Genetic predisposition. This hypothesis was tested in an epidemiological study,[49] where 52 schizophrenic patients were examined for different HLA antigens. There was higher occurrence of HLA-B44 among schizophrenic patients with DIP compared with those with schizophrenia without DIP. This genetic predisposition might explain the variable incidence of side effects among patients taking a similar dosing regimen.[49] Also, some reports have supported familial predisposition, a single heterozygous mutation of the park-2 gene was found in some cases of DIP.[42]

4. Human immuno virus infection. In a retrospective study of 115 HIV patients,[50] 6 had Parkinsonism (5%), 5 out of 6 had DIP. The mean age of the patients at the time of onset of Parkinsonism was 34.5 years. All patients had severe immune suppression with a mean CD4 cell count of 14 cells/mm^3 at the time of diagnosis. Drug-induced Parkinsonism in HIV-infected patients may be the result of underlying preexistent subclinical nigral degeneration. Neuropathology studies have shown reactive gliosis, macrophages, and multinucleated giant cells infiltrate the basal ganglia especially the putamen, caudate nucleus, and substantia nigra.[51,52]

Protective factors. 1. Anticholinergic drugs. It is a common practice that high potency typical antipsychotics are started concomitantly with anticholinergic drugs, and this practice has shown to reduce the occurrence of DIP. A possible explanation for this practice is that increased cholinergic activity will lead to stimulation of the GABAergic inhibitory pathway in the basal ganglia. Although in 1990, the World Health Organization issued a consensus statement recommending against this practice.[51]

2. Smoking. Smoking has a protective effect against idiopathic PD as well as DIP, and that might be attributed to: stimulation of various neurotransmitters (dopamine, acetylcholine, norepinephrine) by nicotine.[52] Tobacco may also act as an monoamine oxidase-B (MAO-B) inhibitor that increases the availability of dopamine.[53]

Pathophysiology of drug-induced Parkinsonism. One of the acceptable and widely adopted theories explaining psychosis observed in schizophrenia is dopaminergic hyperactivity.[54] It is based on the amelioration of psychotic symptoms with antidopaminergic medication and provocation of psychotic symptoms with dopamine agonist treatment.[55] The D2 receptor blockade in the

mesocortical and mesolimbic pathways have an essential therapeutic role in controlling psychotic symptoms, and EPS emerge because of non-selective blockade of D2 receptors in the nigrostriatal pathway.[56,57] Based on the computed positron-emission tomography, 60-80% of D2 blockade is required for antipsychotic effect. If more than 80% of D2 receptors are occupied, DIP will develop.[58,59]

Pathology. There is limited data regarding the histopathological findings in DIP because of the small number of patients undergoing postmortem brain examination. In one study,[60] 8 patients with DIP underwent postmortem autopsy, and 6 were found to have basal ganglia pathology. Basal ganglia pathology was found in 2 out of those 3 patients: vascular lesion in the basal ganglia in one patient and Lewy body disease in the other, indicating that DIP might be simply an unmasked PD.[60] Another pathological finding in this study[61] was Alzheimer disease and frontotemporal dementia (FTD) in some cases.[62,63] In another postmortem study[64] of 2 patients carrying the diagnosis of DIP with symptoms reversal after stopping neuroleptic treatment, the histopathological finding was that of idiopathic PD where there were loss of melamine-containing nerve cells in the substantia nigra, and numerous Lewy bodies with normal striatal dopamine receptor assay in both cases.

Management. The management of DIP should be directed toward careful identification of the high risk population, avoidance of unnecessary prescribed medications, and if needed, wise choice of favorable profile medications (low-potency, small dose medications, and domperidone instead of metoclopramide), use of the lowest dose of causative drugs, and avoid maintenance of these drugs for long periods. Once DIP has developed, withdrawal of the offending medication is required. Usually, symptoms will disappear within a few weeks.[65] However, this may take up to a year or more. In case of severe symptoms that may significantly impact the quality of life, anticholinergic medication can be used since DIP symptoms can respond remarkably to them.[66] Amantadine has shown to be equally effective to anticholinergic medication.[67] Whether anticholinergics or amantadine is used, reassessment after resolution of symptoms should be carried out by stopping the antiparkinsonian treatment and re-evaluating the patient; most DIP symptoms will eventually resolve with time after stopping the culprit agent.

Prognostically, one of the following 3 scenarios will be encountered:[68]

1. Drug-induced Parkinsonism with full recovery. This is the commonly observed outcome, and observed in approximately 70% of cases within 2-4 months, although some symptoms such as tremors may continue for 6-18 months.[68]

2. Drug-induced Parkinsonism unmasks Parkinson disease. This is suggested by persistence of parkinsonian symptoms after withdrawal of the causative drug. This outcome is reported in several series in 5-15% of patients. Interestingly, Burn et al[59] reported abnormal F-dopa PET in all the 3 patients that had persistent Parkinsonism after stopping the offending drugs. These observations support the notion that pre-existing dopaminergic defects in the nigrostriatal pathway becomes clinically overt after challenged with dopamine depleters.

3. Drug-induced Parkinsonism antedates Parkinson disease. This means that some drugs may accelerate the clinical development of asymptomatic degenerative PD. In this case, a period of clinical recovery after discontinuing the medication causing DIP, will precede reappearance of parkinsonian symptoms. This was reported in 5 patients out of 95 that developed PD after a period of recovery of approximately 11 months.[69] It is not clear why patients will go on into a latent period with absence of clinical signs before the re-emergence of extrapyramidal signs and the eventual diagnosis of PD.[70] However, one can conclude that even with initial and complete recovery from DIP, still there is increased risk that the patient will eventually be diagnosed with PD.[71]

In conclusion, DIP is a significant source of disability in the elderly population that is usually overlooked. Physicians should avoid prescribing medications without strong indication, use medication with the least side effects, and at the lowest effective dose. In elderly patients usually on polypharmacy, careful evaluation of all medications, including non-regular medications, and over-the-counter medications is needed to avoid undesirable side effects, contrary to previous beliefs. Even new atypical neuroleptic drugs at high doses may cause DIP.

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