

Drug-induced parkinsonism: diagnosis and management

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Abstract: Drug-induced parkinsonism (DIP) has been known for >60 years. It is the second leading cause of parkinsonism, but still underdiagnosis is likely to influence reported incidence figures. Since DIP is clinically undistinguishable from Lewy-body Parkinson's disease, any new case of parkinsonism should prompt the search for an offending antipsychotic, hidden neuroleptic, or nonneuroleptic agent that may produce DIP. DIP is reversible upon drug withdrawal in most cases. There is no consensus regarding the duration of the recovery period to allow motor signs to fully remit in order to confirm the diagnosis of DIP following removal of the causative agent, but a drug-free interval of at least 6 months is generally recommended. Interestingly, up to 30% of DIP cases may show persisting or worsening motor signs beyond 6 months following drug withdrawal or adjustment, due to complex postsynaptic and presynaptic factors that may variably interact to negatively influence nigrostriatal dopamine transmission in a so-called "double-hit" hypothesis. The condition significantly impacts on quality of life and increases the risks of morbidity and mortality. Management is challenging in psychiatric patients and requires a team approach to achieve the best outcome.

Keywords: neuroleptic drugs, extrapyramidal side effects, second generation antipsychotics, calcium channel blockers, valproic acid, tetrabenazine

Introduction

In view of its prevalence and expected reversibility upon drug withdrawal, drug-induced parkinsonism (DIP) has drawn sustained interest for >60 years. Its causative mechanisms and clinical similarity with Lewy-body Parkinson's disease (PD) have contributed to our understanding of the latter condition and to the discovery of oral levodopa as symptomatic replacement therapy.¹ Although its prevalence is in part related to the aging of the population and expanded polypharmacy,²⁻⁴ an individual variation in susceptibility has long been documented.

DIP was initially described in 1954 by Bergouignan and Régnier⁵ and Steck⁶ in patients treated with chlorpromazine and reserpine, setting aside first-generation classical antipsychotic drugs and monoamine depleters as high-risk offenders. The list of drugs associated with DIP has grown ever since, to extend to gastrointestinal prokinetics, calcium channel blockers, modern atypical antipsychotics, and antiepileptic drugs that impair dopamine function directly or indirectly.¹ Many cases are serious enough to be spontaneously reported to sanitary agencies.⁷ The condition is not reversible in at least 10% of cases and carries a risk of morbidity and mortality particularly in the elderly,⁸ especially if neuroleptic malignant syndrome (NMS) develops. Clinicians must remain wary of its development and manage it diligently.

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Definition and epidemiology

The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-V*),⁹ defines DIP as the presence of resting tremor, muscular rigidity, akinesia, or bradykinesia, developing within a few weeks of starting or raising the dosage of a medication (typically a neuroleptic) or after reducing the dosage of an antiparkinsonian agent. In this definition, the presence of bradykinesia is not mandatory, in contrast to the conventional definition of the parkinsonian syndrome (PS) proposed in the UK Parkinson's Disease Society Brain Bank (UKPDSBB, Step 1) clinical diagnostic criteria.¹⁰ The absolute symmetry of the motor signs is not part of the *DSM-V* definition, but strictly unilateral signs are unusual in DIP (as detailed in Clinical presentation section). Lack of standard criteria for DIP and misdiagnosis rate undoubtedly have a significant impact on epidemiological data. Several scales are available to document DIP, and the most widely used, the Simpson–Angus Scale, largely excludes bradykinesia as a requirement, shifting emphasis on rigidity.¹¹ Using the *DSM* classification, Simpson–Angus Scale, and UKPDSBB Step 1 criteria for PS identification in a group of older adults medicated for chronic schizophrenia, the prevalence of PS was 62.5%, 87.5%, and 39.3%, respectively.¹² In a single academic center, only one of 24 patients with DIP had been properly diagnosed prior to referral.¹³ The reasons for underdiagnosis are several-fold, including lack of recognition or attribution of the clinical presentation to PD or the mental illness (as apathy, depression, catatonia, psychogenic condition). In wrongly ascribed cases, the drug profile may inadequately be deemed inoffensive (eg, low-dose classical antipsychotics, use of atypical antipsychotics in monotherapy, or hidden neuroleptics). In contrast to young patients, people over age 50 years with declining dopamine D2 receptors density may display DIP with estimated D2 receptor occupancy levels <80% in the putamen assessed by positron emission tomography, and a daily dose of risperidone as low as 0.58 mg can achieve 50% maximal receptor occupancy.¹⁴ In other missed cases of DIP, the motor signs may have been mild and asymptomatic, unilateral or asymmetric, or delayed in onset or offset. According to the *DSM* criteria, DIP must become apparent within a few weeks of a change in antipsychotic drug treatment, but there are exceptions. With central dopamine antagonists, most DIP cases develop within 3 months,^{15,16} but drug exposure up to 12 months may be necessary in the case of calcium channel blockers,¹⁶ even longer in valproate users.¹⁷ There is no consensus regarding the duration of the recovery period to allow motor signs to fully remit

and confirm the diagnosis of DIP following removal of the causative agent, but a drug-free interval of at least 6 months is generally recommended.¹⁸ In 17 DIP patients studied retrospectively, ten achieved complete remission after a mean (range 2–19 months) interval of 10 months.¹³

This proof of reversibility is impractical to fulfill in many psychiatric patients who cannot withdraw their medication easily. Of note, some reversible DIP cases may still show Lewy-body pathology at autopsy to raise a diagnosis of unmasked PD.^{19,20}

Keeping these caveats in mind, it should come as no surprise that the prevalence of DIP is variable between studies and highly dependent on the proportion of older adults in the population under study. In the EUROPARKINSON Collaborative Study, DIP was estimated to contribute to 5% of all cases of PS in Europe.²¹ The prevalence in patients treated with classical antipsychotics was reported long ago to vary between 4%¹⁵ and 40%,²² making comparisons between first- and second- or third-generation antipsychotics difficult. In population studies, DIP is generally considered the second leading cause of PS with 22% (door-to-door survey in central Spain),²³ 20% (Rochester Epidemiology Project),¹⁸ and 37% (Bambu study)⁴ of all cases of parkinsonism. In tertiary care movement disorder clinics, the proportion of PS attributed to DIP varies between 4% and 10%.^{13,24} A preponderance of women is often reported, attributed to drug dosing or interaction issues or hormonal influences.^{15,16,18,25–28} In addition to old age and female sex, commonly accepted patient-related risk factors for DIP (Table 1) include preexisting extrapyramidal disorder,²⁹ concomitant brain damage and atrophy,³⁰ dementia,^{29,31} HIV infection,³² severe psychiatric disease,³³ severe unexplained hyposmia,^{34,35} and familial PS,³⁶ while drug-related risk factors include drug potency and dosing maximizing striatal dopamine D2 receptor occupancy in numbers and constancy.

Table 1 Patient-related risk factors for DIP

Risk factors	References
Aging	1,3,15,18,22,23
Female sex	15,16,18,25–28
Preexisting extrapyramidal disorder	29
Brain damage and atrophy	30
Dementia	29,31
HIV infection	32
Severe psychiatric disease	33
Severe unexplained hyposmia	34,35
History of familial parkinsonism	36

Abbreviation: DIP, drug-induced parkinsonism.

In a group of 67 patients with intellectual disability, DIP did not correlate with overt brain damage.³⁷ Dopamine receptor gene variations seem uninvolved.³⁸

Drugs

A strong knowledge of all drugs producing PS is important to raise suspicion about the disorder (Table 2). Many drug

classes are implicated, and clinicians should know about the drugs carrying a risk of DIP in their own field of practice in order to advise and monitor patients under treatment adequately. Drugs associated with DIP may be classified as neuroleptic versus nonneuroleptic, according to their propensity for causing PS or in terms of the pathogenic mechanism of interference of dopamine neurotransmission.^{1,2}

Table 2 Offending agents causing DIP

Class	Drugs	Risk		
Conventional antipsychotics	Phenothiazines	High		
	Chlorpromazine			
	Levomepromazine			
	Thioridazine			
	Perphenazine			
	Fluphenazine			
	Thioxanthenes			
	Flupentixol			
	Thiothixene			
	Zuclopenthixol			
	Diphenylbutylpiperidines			
	Pimozide			
	Dibenzoxazepines			
	Loxapine			
	Amoxapine			
	Butyrophenones			
	Haloperidol			
	Atypical antipsychotics		Thienobenzodiazepine	High
			Olanzapine	
Pyridopyrimidine				
Risperidone				
Dibenzothiepine				
Zotepine				
N-arylpiperazine				
Aripiprazole	Low			
Quetiapine (low-to-moderate dosage)				
Clozapine (low-to-moderate dosage)	Low			
Neuroleptics	Phenothiazine derivatives	Intermediate to high		
	Prochlorperazine			
	Promethazine			
	First-generation H1 antihistamines (hydroxyzine, alimemazine, aceprometazine)			
	Benzamide substitutes			
	Metoclopramide			
	Sulpiride			
	Tiapride			
	Cisapride			
	Clebopride			
	Veralipride			
	Nonneuroleptics		Gastroprokinetic	Low
			Heteroarylpiperidine	
Monoamine depleters	Domperidone	High		
	Tetrabenazine			
Sympatholytic (l-tyrosine derivative)	Reserpine	High		
	Methyl dopa			

(Continued)

Table 2 (Continued)

Class	Drugs	Risk
Calcium channel antagonists	Flunarizine, cinnarizine Diltiazem, verapamil	High Low
Antidepressants	Tricyclics Imipramine Amitryptiline Clomipramine Dosulepin Selective serotonin reuptake inhibitors Serotonin norepinephrine reuptake inhibitors Monoamine oxidase inhibitors Moclobemide Phenelzine	Intermediate Intermediate Low
Inorganic ion	Lithium	Intermediate
Anticonvulsants	Valproic acid Phenytoin	Intermediate
Miscellaneous	Antiarrhythmics Amiodarone Procaine Immunosuppressants Cyclosporine A Acetylcholinesterase inhibitors Chemotherapeutic agents Thalidomide Antibiotics Rifampicin Antiviral (acyclovir, vidarabine, antiretrovirals) Antifungal (amphotericin B) Hormones Thyroxine	Low

Abbreviation: DIP, drug-induced parkinsonism.

Antipsychotic agents

Centrally acting dopamine receptor antagonists accounted for nearly half of all DIP cases in one pharmacovigilance center collecting spontaneous reports.¹⁶ Typical, first-generation antipsychotics with high affinity for dopamine D2 receptors constitute a distinct class, including phenothiazines (eg, chlorpromazine, levomepromazine, thioridazine, perphenazine, fluphenazine), thioxanthenes (eg, flupentixol, thiothixene, zuclopenthixol), diphenylbutylpiperidines (eg, pimozide), dibenzoxazepines (eg, loxapine or its metabolite amoxapine), and butyrophenones (eg, haloperidol). Their risk is likely influenced by their antimuscarinic properties. Several second- and third-generation atypical antipsychotics also cause DIP or may unmask and exacerbate PD.³⁹

Causative agents mainly include olanzapine, risperidone, and aripiprazole, drugs also associated with the development of restless legs syndrome. Well-known exceptions include low-to-moderate doses of the atypical drugs quetiapine and clozapine commonly used safely in PD.^{40–42}

Neuroleptics

Besides antipsychotics, other dopamine receptor-blocking agents are well known to induce DIP. Phenothiazine derivatives (eg, prochlorperazine, promethazine, and first-generation H1 antihistamines such as hydroxyzine, alimemazine, and aceprometazine) and benzamide substitutes (eg, metoclopramide, sulpiride, clebopride, veralipride) used for the relief of nausea, vertigo, or post-menopausal syndrome carry an intermediate-to-high risk of producing DIP. Metoclopramide has a great capacity to accumulate in the substantia nigra, even more so in Alzheimer's disease tissues.⁴³ The gastroprokinetic drug domperidone, which displays strong affinity for dopamine D2 receptors, does not normally cross the blood–brain barrier effectively to block central dopamine transmission.

Nonneuroleptic agents

Drugs interfering with central catecholamines vesicular storage (tetrabenazine, reserpine) or synthesis (α -methyl dopa)

are regarded as high-risk offenders for DIP. Other drugs are in the high-risk category of drugs liable to produce DIP, particularly, the calcium channel antagonists flunarizine and cinnarizine, two drugs bearing a piperazine nucleus displaying dopamine receptor blockade properties and affecting presynaptic dopamine storage and release mechanisms.⁴⁴ Two decades ago, they were leading offending drugs in Japan⁴⁵ and Spain.²⁷ In comparison, the risk is much lower with other cardiotropic calcium channel antagonists such as verapamil and diltiazem, incriminated in a few DIP reports. This may be due to disordered calcium homeostasis affecting vesicular dopamine storage and release and/or to dopamine receptor-blocking properties. Lithium and anticonvulsant drugs (valproic acid in particular and phenytoin) convey an intermediate risk. Lithium adverse motor events may be due to a number of effects, including inhibition of the enzyme glycogen synthase kinase-3 shared with neuroleptics. Chronic lithium administration in older adults has been associated with a higher incidence of antiparkinsonian agent cotreatment.⁴⁶ DIP has been observed in up to 6% of chronic valproate users, representing a tenfold rise in PS compared to the general population.⁴⁷

Lower estimates in the order of 1.37% have also been documented in patients under valproate for 2.5–10 months.⁴⁸ Diagnosis is difficult due to the insidious onset and highly variable treatment interval before motor manifestations emerge, extending to years of valproate exposure in some cases. Patients may even respond to levodopa.¹⁷ The underlying molecular mechanisms remain elusive, possibly involving mitochondrial dysfunction and impaired oxidative phosphorylation.⁴⁹ Serotonergic (5-HT) antidepressants have long been associated with an intermediate risk of DIP (8%),¹⁶ either in monotherapy or with concomitant medications (antipsychotics in particular). Reported cases have involved all classes.^{50,51} These medications do not block postsynaptic dopamine receptors but have been shown to decrease striatal dopamine concentrations in animal studies.⁵² Combination of the antidepressant with an atypical antipsychotic blocking 5-HT_{2A} receptors is not preventive and, to the contrary, may even increase the risk of DIP. Pharmacokinetic interaction at the level of CYP450 metabolism may contribute to raise plasma antipsychotic concentrations.⁵¹ Interestingly, antidepressants have also caused or aggravated restless legs syndrome. Miscellaneous nonneuroleptic drugs have been associated with a low risk of DIP: antiarrhythmics (amiodarone, procaine), acetylcholinesterase inhibitors, antibacterial (rifampicin), antiviral (acyclovir, vidarabine,

antiretrovirals), and antifungal (amphotericin B) antibiotics, and hormones (thyroxine).^{1,2,16} The thiazolidinedione derivative pioglitazone, a peroxisome proliferator-activated receptor-gamma and -alpha receptor agonist, has been reported to negatively have an impact on the motor benefit derived from levodopa in a primate model of parkinsonism,⁵³ but no report of DIP or aggravation of motor symptoms in PD subjects under oral hypoglycemic agents has been published. Anticancer agents generally do not interact with dopamine receptors.⁵⁴ Methotrexate has been shown to reduce brain dopamine levels in rats,⁵⁵ but no DIP cases have been reported to date. The oral 5-fluorouracil prodrug capecitabine reportedly caused an acute dystonic reaction,⁵⁶ but no DIP. Thalidomide worsened PD in one case.⁵⁷ Tamoxifen did not worsen motor function in animal PD models, while relieving levodopa-induced dyskinesia.⁵⁸

Diagnosis and management

Clinical presentation and associated features

It cannot be emphasized enough that DIP is clinically similar to PD, although strictly unilateral motor signs occur in only 4% of DIP cases.⁵⁹ A subacute onset as mentioned in the *DSM* criteria and typically bilateral signs from the outset raise a suspicion of DIP, but signs are reportedly symmetric in 61% of patients.⁵⁹ In another series of 26 autopsy-lacking consecutive patients, motor signs were found asymmetric on the Webster rating scale in 14 (54%) cases.⁶⁰ Thus, asymmetric PS is part of the DIP spectrum and does not necessarily represent underlying PD. Resting tremor is common particularly in the upper limbs (up to 60% in one series¹⁵) but occasionally restricted to the lower lip and jaw (so-called “rabbit syndrome”). An action tremor in both hands may be observed alone or in association with resting tremor. Axial involvement (postural instability, gait disturbance) depends on the severity of the presentation and comorbid brain damage. Slowing of gait is frequent, but freezing is unusual. Almost one-half of DIP cases display additional signs of tardive dyskinesia or akathisia.^{13,60} Pisa syndrome may also be seen, but its frequency is unclear.

In recent years, nonmotor features have been examined with the objective to distinguish DIP from PD. Anosmia and rapid eye movement sleep behavior disorder are not typical of DIP.^{34,61} Abnormal olfactory testing in DIP correctly predicted those subjects displaying persistent signs after drug withdrawal³⁵ or abnormal ¹²³I-metaiodobenzylguanidine (sympathetic neuron imaging ligand) cardiac scintigraphy suggestive of an underlying neurodegenerative process.⁶¹

Rapid eye movement sleep behavior disorder is reported in 15%–60% of PD patients and is suggestive of the diagnosis, although it may be triggered or aggravated by various antidepressants or acetylcholinesterase inhibitors.⁶² Autonomic complaints, including constipation and urinary and sexual dysfunction, are more common in PD than in DIP^{35,63} and relatively more frequent in persistent DIP than in reversible DIP.⁶³ The prevalence of restless legs syndrome in DIP relative to PD is unknown.

Approach

Prevention is the best approach to avoid the acute as well as long-term complications that may occur with all neuroleptic drugs, particularly in subjects at greater risk (Table 1). The indications for antipsychotic drug prescription have broadened tremendously within the last 20 years, in children and in adults alike. In institutionalized elderly with dementia living in Ontario (Canada), the rate of prescription of antipsychotics used for behavioral management has been steadily over 30% in the last decade.⁶⁴ In general, the indication for psychotropic drug dispensing should be reevaluated periodically, and in the case of symptomatic DIP, the drug should be discontinued whenever possible, a recommendation admittedly more easily applicable in nonpsychotic patients. For those who must be kept on antipsychotic drug treatment, prescribers must be aware that polypharmacy with psychotropic drug combinations may raise the risk of DIP due to unanticipated pharmacodynamic and/or pharmacokinetic factors. A change in drug class to a low-dose atypical agent, ideally quetiapine or clozapine, would offer the best chance to reverse the condition and facilitate management in the long run. In the event, DIP remains symptomatic; a team approach with the treating psychiatrist and individualized treatment should be proposed, taking into account the patient age, the severity of the motor condition, and impact on quality of life. Prescribing antiparkinsonian medications may threaten the underlying psychopathology and cognition or exacerbate tardive dyskinesia. The clinical response highly depends on the robustness of the antipsychotic drug regime left in place for maintenance therapy. Thus, mild DIP is probably best left untreated. For the others, an anticholinergic drug or amantadine may be used in individuals under or over 60 years of age, respectively.⁶⁵ Levodopa may be added but reported benefit is variable and often modest,⁶⁰ but those with valproate-induced parkinsonism may respond.¹⁷ Dopamine agonists have also been used,⁶⁶ but detailed studies regarding tolerability are lacking. Physical therapy should be proposed particularly in those with disordered posture and gait.

Other clinical issues

Persistent parkinsonism following neuroleptic exposure

Up to 30% of DIP cases may show persistent or worsening motor signs beyond 6 months following drug withdrawal or adjustment.^{67–69} In a French elderly cohort of 2,991 noninstitutionalized individuals, neuroleptic exposure increased 3.2-fold the risk to develop probable PD.⁷⁰ The risk was significant for benzamides and the calcium channel blockers flunarizine and cinnarizine. The estimated population-attributable fraction of PD associated with drug exposure suggested that avoidance of drug exposure would yield a 21.7% reduction in the number of new cases of PD. In the last 15 years, studies using single photon emission computed tomography and dopamine transporter ligands have examined the integrity of the nigrostriatal dopamine terminals in DIP, revealing reduced binding capacity in >40% of cases.⁷¹ The underlying pathogenic explanation for these results is lacking, since several autopsy cases of DIP patients under long-term antipsychotic drugs have shown no significant substantia nigra pathology.^{19,20} Thus, postsynaptic and presynaptic factors may variably interact to influence nigrostriatal dopamine transmission and contribute to persistent DIP in the context of chronic neuroleptic exposure. In a recent review, this “double-hit” hypothesis was proposed to involve drug-induced neurotoxic cell death with inhibition of the mitochondrial respiratory chain, free radicals production, and lack of trophic support.⁷² Further studies are required to shed light on the mechanisms at play.

Neuroleptic malignant syndrome

Parkinsonism as part of the NMS is an infrequent drug side effect, with prevalence estimates averaging 0.991 cases per thousand people.⁷³

Rigidity typically coexists with fluctuating delirium, fever, and dysautonomia and is associated with a rise in creatine phosphokinase (usually >1,000 IU/L) and white blood cell count in most cases.⁷⁴ Like DIP, NMS commonly arises within the first few days or months following drug initiation or upward titration, but it can occur at any time point during exposure. All neuroleptics may trigger NMS, and high dosing as well as polypharmacy (combination of antipsychotics or adjunct therapy with lithium or carbamazepine) constitutes pharmacological risk factors, whereas environmental factors include physical restraint and dehydration. Profoundly altered dopamine transmission due to extensive D2 receptor occupancy in the basal ganglia⁷⁵ and hypothalamus (disturbing thermoregulation), as well as musculoskeletal fiber toxicity,

are thought to contribute, but current knowledge on precise mechanisms is lacking. Prompt recognition and withdrawal of the offending drug are important to prevent complications and mortality. Supportive treatment and use of dantrolene and dopamine agonists are common practice.⁷⁶ Other agents such as amantadine, levodopa, and benzodiazepines have been tested. Dantrolene should be stopped as soon as possible, and the dopamine agonist maintained for 10 days (if harmful neuroleptic oral) or 2–3 weeks (if harmful neuroleptic depot). Reintroducing an antipsychotic may be considered at least 2 weeks after clinical recovery.

Conclusion

The motor features of DIP are clinically indistinguishable from Lewy-body PD. Thus, DIP requires a high index of suspicion and knowledge of the diverse offending drugs in order to be managed effectively. The condition significantly impacts on quality of life and increases the risks of morbidity and mortality. It is more complex than heretofore believed, with acute and chronic pictures documented and a variable interplay between nigrostriatal presynaptic and postsynaptic mechanisms implicated in different patients. Nonmotor features such as anosmia and cardiac denervation examined by ¹²³I-metaiodobenzylguanidine scintigraphy may distinguish pure reversible DIP from PD. Autopsy findings in reversible or irreversible DIP have shown Lewy-body midbrain pathology and neuronal loss in a fraction of cases only, leaving many cases unexplained. DIP management is challenging and requires a team approach with the treating psychiatrist to achieve the best outcome.

Disclosure

In the last 3 years, PJB has received honoraria as consultant and speaker from UCB Pharma Canada, and as speaker from Novartis Pharma Canada. VK reports no conflicts of interest in this work.

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