

Title page

Title: The risks of drug-induced parkinsonism/tardive dyskinesia in the elderly and current methods to overcome it.

Running title: Drug induced parkinsonism & tardive dyskinesia in the elderly.

Authors:

Estévez Fraga, Carlos¹, López-Sendón Moreno, Jose Luis².

1. Department of Neurodegenerative Diseases. UCL Institute of Neurology. London.
2. Department of Neurology. Hospital Ramón y Cajal. Madrid.

Corresponding author: López-Sendón Moreno, Jose Luis.

Address: Department of Neurology. Hospital Ramón y Cajal. Carretera de Colmenar Km 9.100 SN.

ZIP: 28034. Madrid (SPAIN):

Telephone: 0034-913368821.

Email: jlopezsendon@salud.madrid.org

Abstract:

Drug induced parkinsonism and tardive dyskinesia are iatrogenic consequences of the use of antidopaminergic drugs. Both entities share risk factors, physiopathological mechanisms and to some degree, therapeutic approaches.

Here we review both entities and discuss emerging therapies including the recently approved drug deutetrabenazine and relevant aspects for clinical practice such as new diagnostic techniques.

Key points:

- Drug induced parkinsonism and tardive dyskinesia are iatrogenic consequences of the use of antidopaminergic drugs.
- DIP is considered a direct consequence of the blockage of D2 receptors while TD has a more complex physiopathology, including enhanced sensitivity of dopamine receptors.
- Both entities are more frequent in older people due to a progressive loss of dopaminergic neurons with age.
- New therapies are available for TD, including deutetrabenazine.

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The risks of drug-induced parkinsonism/tardive dyskinesia in the elderly and current methods to overcome it.

1.- Introduction

Tardive dyskinesia (TD) and drug-induced parkinsonism (DIP) are iatrogenic disorders caused by dopamine receptor blockers (DRB) [1]. They were recognized early after the introduction of antipsychotics[2] to the clinical practice, leading to the finding that DIP caused by reserpine, a dopamine depletor, was related to dopamine deficiency [3].

Elderly patients are more susceptible to these side effects, probably due to an age-related decrease in nigral neurons and dopamine[4]. Since the introduction of newer second generation antipsychotics (SGA) the frequency and intensity of these side effects has improved [5].[6].[7].[8] but there is still room for concern [9],[10].TD and DIP share risk factors, pathological mechanisms and management, and might coexist in one given subject. Latest available evidence has clarified some intriguing features of TD and DIP. Meanwhile, new medications to treat TD are now available, highlighting the importance of a thorough, updated, knowledge of this pathologies.

This article offers a comprehensive review of the incidence, clinical features and mechanisms behind DIP and TD. The benefits and risks of previous available drugs and those that have been recently approved by regulatory agencies are discussed.

2. Drug induced Parkinsonism

2.1 Definition

DIP occurs when symptoms emerge after exposure to drugs, usually those that either deplete dopamine storages [11] or block dopamine receptors[12]. By definition, symptoms should be reversible, six months after the offending agent has been withdrawn[13] but actually up to 20% of patients develop persistent deficits despite drug discontinuation[14] leading to the hypothesis that these patients might have subclinical Parkinson's Disease (PD) unmasked by neuroleptic exposure (umPD), complicating the differential diagnosis [15], especially between aged patients, who are more prone to both PD and DIP.

2.2 Epidemiology and risk factors

After PD, DIP is the most common cause of parkinsonism [16]. Prevalence and incidence rates of DIP vary depending on the population studied and the ascertainment method [17]. A door-to-door study in Spain [18] found DIP as the third most common cause of parkinsonism with a global prevalence rate of 2% between patients older than 65 years. The Rotterdam study, a prospective population-based cohort study concluded that DIP was responsible for 12% of all causes of parkinsonism [19] whereas another cohort study, found that DIP was the second cause for parkinsonism (32.3%) after PD [20] Recently Savica et al analyzed the incidence and time trends of DIP over 30 years in Olmsted

County, Minnesota. The authors found an annual incidence rate of 3.3 per 100000 persons-years showing that it had decreased 30% during the last decade [21].

Globally, about 15% of patients on antipsychotics develop DIP after long-term therapy and this proportion exceeds 50% among subjects over 60 years [22] [23].

The main risk factors predisposing to DIP are either related to the patient or to the drug that is responsible for the symptoms.

In the different studies, age, has been shown to be as a consistent risk factor. Prevalence increases from 9.4 in patients between 60-69 years until 29.3 in those between 80-99, [21] [24] possibly through and age-related decline in the number of neurons of the nigrostriatal system [25] Another individual-related risk factor is the presence of dementia, a condition that affects mostly old populations having an incidence rate of 67% of DIP [26] . Likewise, sex has a modifying effect on DIP prevalence, with a higher incidence in women [27] [28].

On top of that, there is marked individual variation. This suggests that genetic predisposition might play a role in the development of DIP. Shiroma et al showed genetic polymorphisms in genes involved in dopamine transmission [29] whereas Metzger et al found a higher prevalence of HLA antigen B44 in DIP patients [30] and there have been described families with a hereditary predisposition to DIP [31].

Many drugs have been described to cause parkinsonism but there are several factor that modulate this risk. Neuroleptics are well known causes of DIP with potency and dose being unequivocal risk factors [23]. First generation antipsychotics (FGA) might trigger symptoms even at low doses while SGA or rarely causing symptoms.

2.3 Pathophysiology and causal agents (Table 1)

Virtually any agent that blocks the postsynaptic D2 receptors or depletes presynaptic dopamine has the potential to cause parkinsonism [32] [33]. Most common causal agents are antipsychotics and dopamine depleting drugs, but other medications with antidopaminergic effects such as antiemetics, as well as antihistaminics and calcium channel antagonists are often causes for DIP.

Calcium channel blockers are between the commonest drugs related to DIP reaching up to 40% of the cases in some series [34]. They affect elderly patients possibly through its affinity for blocking the D2 receptor which is similar to atypical antipsychotics [35] [36]

Substances as lithium, valproic acid or amiodarone cause parkinsonism due to unknown mechanisms [23][37]. Serotonin selective reuptake inhibitors (SSRIs) might rarely produce DIP, but due to the frequency of its use in general medical practice its contribution should always be considered[38]. Strikingly not all antipsychotics cause DIP. Quetiapine, does not appear to worsen parkinsonism [39]

whereas clozapine has even been reported to improve PD motor symptoms, possibly through its 5HT-2A activity and rapid dissociation of the D2 receptor[40][41]

Furthermore, dopamine blockade itself does not completely account for DIP since symptoms last for weeks to months, whereas the effect of neuroleptics over psychosis last only for several hours [42]. Reserpine was the first presynaptic vesicular monoamine transporter inhibitor (VMAT), acting on both the central and peripheral isoforms, producing marked side effects [43]. Tetrabenazine (TBZ) was the first selective VMAT2 inhibitor. Developed initially as an antipsychotic to treat schizophrenia [44]. However, it was rapidly recognized to be effective against hyperkinetic movements and in 2006, following the publication of the TETRA-HD study, it was approved for the treatment of chorea associated with Huntington's Disease [45]. Depression (15%), and parkinsonism (12%) are dose-dependent side effects[45] possibly due to its short half-life [44].

Recently, new highly selective VMAT2 inhibitors have been developed. Valbenazine has shown to improve TD in the KINECT 3 trial [46]. In this study parkinsonism was an exclusion criteria, and results disclosed no differences between treatment groups both after 6 weeks and after a 1-year period in parkinsonism as assessed by the Simpson-Angus-Scale [47]. With a similar mechanism of action, deutetrabenazine has showed in 2 studies, one in a population with chorea associated with Huntington's Disease and other in patients suffering TD similar DIP rates in both treatment and placebo arms. Outcome measures were the parkinsonism items of the UHDRS scale and the UPDRS [48]. However, some methodologic concerns have been raised regarding published post-hoc comparisons with TBZ [49].

Neuroleptics might possibly bear intrinsic neurotoxicity over dopaminergic systems instead of merely unmasking preexisting PD[15]. This is supported by increased long-term risk of incident PD after past exposure to neuroleptics whilst with only 30% of patients develop parkinsonism during exposure [50]. This is supported by animal models which suggest that exposure to neuroleptics induces dopaminergic neuron death through inhibition of mitochondrial respiratory chain, increased dopamine receptor turnover and free radical production [15].

There is also data suggesting that parkinsonism developing shortly after exposure to neuroleptics is associated with subtle underlying nigrostriatal dysfunction. Chung et al performed DaTscans in 71 patients with DIP from South Korea who had visually normal functional imaging. Only when quantitative analysis was performed it was possible to observe a statistically significant reduction in DAT availability in those who presented parkinsonism less than 6 months after initiation of neuroleptics. In contrast, no alterations were found in subjects with late-onset parkinsonism, suggesting that early-onset DIP might be in fact umPD [51]In addition, one clinico-pathological study in 7 patients with DIP did not report any relationship between presence of Lewy bodies and symptom reversal [52].

In conclusion, complex mechanisms, where an interaction between subjects' predisposing factors and biochemical properties of offending agents account for the appearance of DIP. Whether or not chronic use of neuroleptics may cause morphological changes in the brain is still a matter of debate.

2.4 Clinical features and diagnosis (Table 2)

DIP is frequently under-recognized. Common etiological agents such as SGA and antiemetics do not appear to be well-known causes for DIP [53]. Although current treatment with neuroleptics is an exclusion diagnostic criteria for PD [54], there are not officially established time periods for drug washout after detection of DIP. However, it is generally accepted that symptoms should recover within 6 months after drug withdrawal [13].

There are some clinical features and ancillary testing that might help differentiating DIP from PD (*Table 2*) such as acute onset, symmetry of symptoms, absence of rest tremor, presence of orolingual dyskinesias or akathisia which point towards DIP. Moreover, recent literature review by Brigo and colleagues suggest that non motor symptoms, specially anosmia, urinary and sleep problems, if assessed systematically help orientating diagnosis [55].

Sustancia nigra hyperechogenicity assessed by transcranial sonography could be an useful prognostic marker [56] but possibly abnormal DaTscan, is the best predictor for the differential diagnosis of PD and DIP with a higher proportion of DaTscan + patients developing persistent symptom [57,58],[59,60]. Furthermore, cardiac 123I-MIBG scintigraphy [61] has shown to be altered in those manifesting persistent parkinsonism [62] in patients with abnormal smell function at baseline [63] and in those who develop parkinsonism years later [62], suggesting the diagnosis of unmasked PD rather than DIP.

Therefore, meticulous physical examination and clinical history should be warranted in order to assess patients, whereas ancillary testing might be requested when in doubt after cessation of the offending drugs.

2.5 Prevention and treatment

2.5.1 Prevention

Prevention is the most important factor. Using SGA, at the lowest effective doses and always monitoring for signs of parkinsonism, especially in high risk patients, is essential [17].

Prophylaxis with anticholinergics has reported conflicting results and it is not recommended [64] [65].

2.5.2 Management.

DIP should be treated only if it affects patients in their daily living activities. First option should be, if possible, either lowering the dose or switching to a less potent antipsychotic. If clinical scenario does not allow these changes, or they are ineffective, anticholinergic drugs should be the next choice. Despite most evidence coming from low quality studies with small numbers of patients and subjective methods of assessment where efficacy has been possibly overestimated [32] [66] positive results and wide experience favours its use in DIP [67] [68].

Immediate-release amantadine has been during several years the main drug with an antidyskinetic effect in PD [69] [70]. It has been tested in several small clinical trials suggesting benefit in patients with

DIP [71]. More recently, extended-release amantadine received FDA approval (Gocovri) for PD dyskinesia [72] but there are yet no reports regarding its use in DIP.

Levodopa and dopamine agonists are usually ineffective. However, parkinsonism in the context of presynaptic dopamine depleters or in unmasked PD is expected to improve with levodopa [73].

Ultimately, electroconvulsive therapy (ECT) can achieve rapid improvement of symptoms both in DIP and in PD and it might be of benefit when there are coexistent mood disorders or psychosis [74].

Figure 2. Management of DIP.

3. Tardive syndromes

3.1 Definition

Tardive syndromes (TS) are characterized by abnormal involuntary movements caused by chronic exposure to DRBs [75]. The movements appear lately during treatment course and tend to persist during long periods of time, occurring in a variety of phenomenologies being rhythmic oral-buccal-lingual (OBL) chewing movements the most typical presentation [76], therefore the term “tardive dyskinesia” have been reserved for this type of movements, whereas other syndromes should be named based on the specific phenomenology, reserving TS for the frequent combination of different movement disorders. However, most studies refer to TD without further specifications.

3.2 Epidemiology and risk factors

The prevalence of TD oscillates from 0.5% to 65%[77];[78] of patients treated with neuroleptics. These differences account for the heterogeneity of the different populations studied, as well as the intrinsic variability of the disorder. Most authors estimate the mean prevalence to be between 20-50% based on large prospective cohort studies [78]. The incidence seems to increase with longer exposure times: Caligiuri and colleagues showed a cumulative incidence of TD from 2.5% after 1 year of treatment until 22.9% after 3 years [79] [80]. In addition, the Hillside study beginning in 1977 found that after 10 years 43 % of patients treated FGA developed TD [81]

A recent meta-analysis across 41 studies including a total of 11.493 psychiatric patients showed that global TD prevalence was 25.3%. Prevalence rates varied according with the type of antipsychotics being 20% between those under treatment with SGA compared to 30% in patients treated with FGA[82]. However, Woods et al assessed 352 schizophrenic patients during a 4-year period finding an annual incidence of 0.056 in patients with FGA compared to 0.059 in patients with SGA [83]. Globally, despite the increasing use of SGA [6], the last prevalence studies have yielded conflicting results[9];[84];[85].

In addition, there are individual factors that increase the risk for TD. Similarly to DIP, age is the most consistent risk factor for the development and maintenance of dyskinesia with rates increasing 3 to 5 fold risk when compared to younger patients [86,87].

Female sex increases the risk of TD [77] possibly through oestrogens' antioxidant and dopamine modulating properties [88]. Non-white ethnicity also predisposes for the development of TD [89] [90]. Genetic polymorphisms in genes related to the dopamine pathway also influence the risk of TD[91].

Besides neuroleptics, other antidopaminergic agents may cause TD. Metoclopramide, an antiemetic, and veralaprindol, used to treat perimenopausal syndromes, are major causes of TD especially in higher doses [92]. Although rare, other non antidopaminergic drugs have been described to produce TD such as antidepressants (SSRIs, and TCAs) [93,94] antiepileptic drugs, [95] antihistaminics [96], oral contraceptives and amphetamines[97].

3.3 Pathophysiology

Despite the early development of animal models showing vacuous chewing movements (VCM) after exposure to haloperidol [98,99] pathophysiology of TS remains obscure. TD are believed to be a consequence of the hypersensitivity and up-regulation of dopamine D2 receptors due to their chronic blockade [100] of antidopaminergics. D2 receptors are inhibitory for the indirect pathway, thus, hypersensitivity and increase in its number produces hyperkinesia. This hypothesis is also supported by the observation that increasing blockade can alleviate symptoms of TD whereas abrupt withdrawal might prompt the appearance of symptoms. However, it cannot explain its persistence up to years after drug withdrawal [88]. Conversely, sustained DRB use increases free radicals formation leading to increased dopamine turnover, [101] neuronal loss and gliosis in the basal ganglia causing persistence of symptoms [102] In fact, postmortem animal studies have shown data consistent with this hypothesis[103].

Likewise chronic blockade of D2 and hypersensitization is followed by maladaptive plasticity in cortico-striatal pathways due to oxidative stress. This alteration results in an imbalance between direct and indirect pathways that contributes to the abnormal output to the sensorimotor cortex perpetuating TD [104]

Since most patients taking antipsychotics do not develop TD genetic susceptibility is possibly involved in TD mechanism [88]. Steen et al have shown that homozygosity for the Ser9Gly variant in the dopamine D3 receptor is present in 22-24% of patients with TD compared with 5% of controls [105]. On the other hand, one meta-analysis of genetic studies indicates a protective effect of polymorphisms in COMT and mnSOD genes [106].

More recently, optogenetic stimulating techniques have shown the involvement of striatal cholinergic neurons and GABAergic D2 medium spiny neurons modulating VCM in mice, suggesting involvement of nicotinic receptor[107][108] implicating further neurotransmitters in the pathophysiology of TD.

3.4 Clinical features

The symptoms of TD typically arise more than one year after DRB exposure. Its emergence frequently follows abrupt discontinuation of the drug, switch in DRB or reduction in dose [88]. TD have an insidious onset over days to weeks followed by plateau of symptoms and thereafter a waxing and waning course but generally persisting during decades. Chronicity depends highly on a prompt detection and management, with remission rates oscillating between 5-90% [109–111] depending on the date of DRB withdrawal. However, once it appears TD does not become more severe if DRB is continued [112].

Phenomenology is highly diverse. In classic TD, the mouth adopts repetitive chewing movements with occasional smacking and opening of the mouth and tongue protrusion. Movements are usually repetitive

and coordinated while they can be suppressed if asked to do so. Despite its striking appearance, patients are often unaware of their symptoms[76] .

Akathisia, another form of TD, is more common in younger patients and consists of a feeling of inner restlessness resulting in inability to sit or stand still. Patients are seen constantly moving with crossing and uncrossing of the legs, trunk rocking, moaning and groaning[75,113,114]. Tardive dystonia also tends to occur during early adulthood. Retrocollis, trunk arching with internal rotation of the arms with extension of elbows and flexion of the wrists are key features for differentiating tardive dystonia from primary dystonias[115].

Chorea as a tardive syndrome usually accompanies OBL dyskinesia but, when in isolation it is known as “tardive chorea”.

“Tardive tremor” has also been described, presenting with slow frequency and low amplitude [116].

“Tardive tics”, indistinguishable from Tourette’s Syndrome [117] and “tardive myoclonus” affecting upper extremities [118] have been described as well. Stereotypies have been equivocally defined as they have been confounded with classical TD[75].

Pain, in oral and genital regions becoming sometimes a source of profound distress, known as “tardive pain” is another complication of treatment with DRB [119].

Tardive parkinsonism is a term used when parkinsonism lasts for years after drug discontinuation and DaTscan is unremarkable [120] with one report disclosing absence of PD pathology. However possibly most cases are related to slightly abnormal functional neuroimaging [51].

Most times however a combination of different phenomenologies is present. Therapy should be targeted towards the main movement disorder. In addition, differential diagnosis should always take into account the possibility of primary neurological diseases with prominent diskinesic manifestations such as Wilson’s disease, Chorea-acanthocytosis or Huntington’s disease. Thorough clinical history and treatments are therefore warranted.

3.6 Prevention and treatment (Figure 2)

Since TS are iatrogenic disorders, prevention is essential. The clinician should avoid treatment with DRB when unnecessary, assess regularly the presence of TS as well as using the smallest effective doses of DRBs. This applies especially in those at higher risk for TS such as elderly patients[86]. Once a TS has been identified the first step should be lowering the dose and eventually removal of the causing agent[76,103,109,121]. This may lead to a transient increase in the severity of dyskinesias, therefore, slow tapering is strongly encouraged [122]. In addition, restarting or increasing the dose of DRB might lead to transient improvement of symptoms, but this approach should be used only in emergency situations.

The approach of discontinuation of DRBs has been questioned in a recent metaanalysis which included two very-low-quality trials involving 17 patients with unclear results[123]. However, in the absence of solid evidence, withdrawal of the offending drug appears reasonable in a drug-induced pathology.

If the patient requires continuous treatment with antipsychotics, switching to SGA, especially clozapine and quetiapine should be the first option, since high doses might be effective for the treatment of TS

[124,125] despite most evidence coming from small, low quality studies (Bergman 2018). In addition, it is possible that the antidyskinetic effect of those drugs at high doses is caused by D2 receptor blocking. In case further treatments are needed, VMAT2 inhibitors should be the first option. Tetrabenazine studies have provided positive results, with improvements in up to 95 % of patients treated [126]. Nevertheless, most studies were small with methodological flaws [127]. TBZ may have dose-limiting side effects such as depression, akathisia and parkinsonism [126].

In the KINECT 3 study a double-blind trial in 205 psychiatric patients, valbenazine showed statistically significant changes from baseline in the Abnormal Involuntary Movements Scale (AIMS) dyskinesia scores, from -3.2 in the 80 mg/day group to -0.1 in controls being well-tolerated [46]. Following this results FDA-approval took place during the same year [128]. The 1-year follow-up study showed no risk of suicidal ideation worsening akathisia or parkinsonism [47].

The ARM-TD study investigating the role of deutetabenazine was also published in 2017. Deutetabenazine has a similar structure to TBZ, but adding deuterium, which leads to decreased plasma fluctuations. This randomized, double-blind study during a 12-week period including 117 psychiatric patients disclosed a statistically significant reduction in AIMS scores from -3.0 in the treatment group vs -1.6 in the placebo arm without substantial side effects [42].

However, despite the positive outcomes in both KINECT 3 and ARM-TD, results should be taken with caution. The chronic course of TD requires longer follow-up in order to establish the safety and efficacy of novel VMAT2 inhibitors.

Anticholinergics have been used in the treatment of TS, but they might have opposite effects on tardive dystonia and TD [88], improving the first one but worsening OBL dyskinesias. Moreover, a recent Cochrane review could not make a confident statement about the effectiveness of anticholinergics (or its withdrawal) in the treatment of antipsychotic-induced TD [129]. Frequent side effects are markedly disabling between the elderly, precluding its use in patients over 60, in particular among those with dementia.

Other less studied medications may provide some degree of symptomatic improvement in TD and have been included in the AAN evidence-based guidelines published in 2013. They found clonazepam and ginkgo biloba probably effective for TD. Amantadine, a glutamate receptor antagonist might be considered for the treatment of TD, when used conjointly with an antipsychotic during the first 7 weeks [130]. Extended-release amantadine remains yet to be studied in TD [131].

Other drugs such as levetiracetam, acetazolamide, baclofen, vitamin E, cholinergic agents, dopamine agonists do have insufficient data according to support or refuse their role in TD according to the AAN guidelines [130].

Despite insufficient evidence, botulinum toxin injections into the muscles causing focal dyskinesia are also recommended in the treatment of TD [132]. There are also case reports supporting the use of globus pallidus interna (GPi) deep brain stimulation in the treatment of severe, refractory TD with up to 50% improvement in symptoms in the majority of cases [133].

Additionally, some exciting new therapeutical approaches are in the pipeline. One of the most appealing is nicotine, which itself has shown to decrease VCM in rodents, whereas nAChR agonist varenicline showed that it reduced VCMs in a dose-dependent fashion [134].

4. Conclusions.

With and increasingly aged population and increasing dementia rates a widespread use of antipsychotic treatments is warranted [135]. Despite recent advances in the understanding of both TS and DIP these conditions are frequently a puzzling problem for the clinician. Although newer treatments are available, only prevention and early detection guarantee a favourable prognosis. It is therefore essential to be aware of these usual side effects of commonly prescribed drugs. Latest evidence shines a light in the complex mechanisms of TD and DIP, but there are still some areas that require urgently further research, eventually aiming to the development of newer therapeutic strategies and contributing to a better understanding of the basal ganglia's physiology and pathophysiology.

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Potential Risk of DIP	Pharmacological group	Drug
High	Dopamine D2 receptor blockers Dopamine depleters (classic) Dopamine synthesis blockers Calcium channel antagonists (P-channel)	Typical antipsychotics Atypical antipsychotics (high doses) Tetrabenazine, reserpine Metildopa Flunarizine, cinnarizine
Intermediate	Atypical antipsychotics Calcium channel antagonists (L-channel) Antiepileptics Antiemetic and gastric motility agents Mood stabilizers	Ziprasidone Diltiazem, verapamil Valproate, phenytoin, levetiracetam Prochlorperazine, metoclopramide, substituted benzamides Lithium
Low	Dopamine depleters (novel) Antiarrhythmics Immunosuppressants Antidepressants Antibacterials Antivirals Statins Antifungals Hormones	Deutetrabenazine, vbenazine Amiodarone, procaine Ciclosporin, tacrolimus SSRIs: fluoxetine, sertraline Tricyclic: phenelzine MAOIs: moclobemide, phenelzine Cotrimoxazole Aciclovir, vidarabine, anti-HIV Lovastatin Amphotericin B Levothyroxine sodium, medroxyprogesterone, epinephrine (adrenaline)

DIP = drug-induced parkinsonism; MAOIs = monoamine oxidase inhibitors; SSRI = selective serotonin reuptake inhibitors.

Main features	DIP	PD
Age at onset	Elderly	Sixties
Symptoms at onset	Symmetrical	Asymmetrical
Onset	Acute or subacute	Chronic
Course with treatment	Reversible	Progressive
Response to causative drug withdrawal	Variable	Poor
Response to levodopa	None	Excellent
Other features	Orolingual dyskinesia, akathisia	
NMS	Uncommon	Common
Rest tremor	Uncommon	Common
Sex	Females	Males
Freezing	Uncommon	Common
Imaging	DatScan: - Cardiac MIBG: - TCS: -	DatScan: + Cardiac MIBG: + TCS: +

Table 1. Main differential between DIP and PD. DIP: drug-induced parkinsonism. PD: Parkinson's disease. NMS: Non Motor Symptoms. DaTscan = Dopamine agonist Transporter scan, MIBG: Metaiodobenzylguanidine. TCS: Transcranial sonography



