Recent developments in drug-induced movement disorders: a mixed picture

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A large and ever-growing number of medications can induce various movement disorders. Drug-induced movement disorders are disabling but are often under-recognised and inappropriately managed. In particular, second generation antipsychotics, like first generation agents, are associated with potentially debilitating side-effects, most notably tardive syndromes and parkinsonism, as well as potentially fatal acute syndromes. Appropriate, evidence-based management is essential as these drugs are being prescribed to a growing population vulnerable to these side-effects, including children and elderly people. Prevention of the development of drug-induced movement disorders is an important consideration when prescribing medications that can induce movement disorders. Recent developments in diagnosis, such as the use of dopamine transporter imaging for drug-induced parkinsonism, and treatment, with the approval of valbenazine and deutetrabenazine, the first drugs indicated for tardive syndromes, have improved outcomes for many patients with drug-induced movement disorders. Future research should focus on development of safer antipsychotics and specific therapies for the different tardive syndromes and the treatment of drug-induced parkinsonism.

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Introduction

Drug-induced movement disorders from prescription medications are common, sometimes go unrecognised, and are often inappropriately managed. The most common drugs to cause these side-effects are dopamine receptor blocking agents, primarily antipsychotics and antiemetics, including metoclopramide and promethazine. Compared with first generation antipsychotics (FGA), second and third generation antipsychotics,[1,2] or so-called atypical drugs, are perceived as safer with respect to the occurrence of drug-induced movement disorders. This is because of speculations over mechanisms of action, high affinity dopamine D_2 receptor and central serotonin-2A (5-HT2A) antagonism, fast D_2 dissociation, and D_2 partial agonism. FGA have stronger D_2 receptor affinity than second and third generation antipsychotics or atypical drugs and is thought to relate to the development of drug-induced movement disorders. Some atypical agents have more affinity for the receptor, whereas others have faster dissociation with D_2 receptors and others partial D_2 agonism and antagonism—it is these features that are hypothesised to result in fewer side-effects. In this Review, second and third generation antipsychotics, such as aripiprazole and brexpiprazole, will be collectively referred to as second generation antipsychotics (SGA) since they are often combined in comparative studies.

The perception of reduced risk of drug-induced movement disorders associated with SGA has resulted in greater, often off label, use, which likely offsets any improved safety. Between 1997 and 2011, there was more than a three-fold increase in antipsychotic prescriptions in the USA.[3] This figure suggests that at least 5 million people are exposed to antipsychotics each year.[4] About 20% of nursing home residents in the USA are on antipsychotics.[5] The trend in overprescribing extends to children and adolescents. Data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey showed nearly a ten-fold increase of SGA prescriptions among patients aged 4–18 years between 1993 and 2010, with 65% of those involving off label prescribing.[6,7] Despite attempts to decrease the use of antipsychotics in the elderly population, and even with the reduction in use of antipsychotics being a quality metric for care for the US federal government, overprescribing antipsychotics to residents with dementia in nursing homes continues to be a widespread problem.[5] Similar trends have been reported in Europe and Canada. For example, the 2017 Agenzia Italiana del Farmaco report showed that the use of antipsychotic drugs had increased from 8·2 defined daily dose (DDD) per 1000 population per day in 2013, to 9·3 DDD per 1000 population per day in 2017. In Canada between 2005 and 2012, there was a 300% increase in primary care or family practice physicians dispensing prescriptions for quetiapine, many of which were for sleep problems and anxiety.[8]

Therefore, drug-induced movement disorders caused by antipsychotics (panel 1) remain relevant to clinical practice. In this Review, we discuss advances during the past 5 years. We review research on tardive syndromes, the latest epidemiological data, and treatments for these syndromes, as they are chronic, irreversible, and often disabling. We also cover new evidence on drug-induced parkinsonism, for which new diagnostic tools are available. Last, we include updates on acute dystonia, akathisia, drug-induced tremor, movement disorders caused by other drug classes, and movement disorder emergencies, which are less common but also have had new advances.

Tardive syndromes

Epidemiology

Tardive syndromes are common but underreported.[9] A meta-analysis[10] on prevalence of tardive syndromes combined 41 randomised controlled trials that prescribed FGA and SGA for psychotic disorders from 2000 to 2015 (n=11 493). Prevalence of tardive syndromes was 21% for SGA and 30% for FGA, which were significantly different

Panel 1: **Movement disorders caused by dopamine receptor blocking agents**

1 Delayed onset and persistent
Tardive syndromes
- Classic tardive dyskinesia
- Stereotypies
- Chorea
- Dystonia
- Akathisia
- Tics
- Tremor
- Myoclonus
- Pain and other sensory phenomena
- Vocalisations
- Mixed tardive syndromes

2 Subacute onset, chronic reversible disorders
- Drug-induced parkinsonism
- Acute or subacute akathisia

3 Acute onset, reversible disorders
- Acute onset dystonia
- Neuroleptic malignant syndrome

(p=0·002). In 20 of the studies that directly compared the two classes of drugs, the prevalence was 25% for SGA and 30% for FGA, a significant difference (p=0.0100). However, when the analysis was restricted to patients who had only been treated with SGA and never had exposure to FGA, prevalence was 7%. A meta-analysis of 57 randomised controlled trials with 32 groups of patients (n=3 763) using FGA and 86 treatment arms (n=15 092) using SGA showed an annual incidence of tardive syndrome for FGA of 6·5% (95% CI 5·3–7·8%) compared with 2·6% (95% CI 2·0–3·1%) for SGA.[11] Although the relative risk of tardive syndromes is less with SGA than with FGA, the risk is not negligible and because SGA are more widely prescribed the absolute number of new cases of tardive syndromes is likely to be increasing.

With regard to course and reversibility of tardive syndromes, observational studies show that, for 2–65% of patients receiving any antipsychotics who had tardive syndromes, the condition improved or remitted over time, mostly in patients who maintained antipsychotic treatment.[4] But in a study with 108 patients with tardive syndromes Fwho were exposed to dopamine receptor blocking agents for a mean of 4·8 years and followed up for a mean of 3·7 years, only 14 (13%) remitted.[12] This study was different because all patients discontinued the causative drug. Because of the high prescription rate, frequency, and low reversibility, tardive syndromes are an important clinical issue and vigilance is advised for all patients treated with dopamine receptor blocking agents.

Clinical phenomenology

Tardive syndrome is a chronic movement disorder caused by treatment with dopamine receptor blocking agents. The onset of symptoms typically occurs during treatment or within 6 months of discontinuation.[13] To distinguish from withdrawal dyskinesia, which occurs because of reduction or discontinuation of dopamine receptor blocking agents, the movements of tardive syndrome should be present for at least 1 month[13] and persist. Most cases are characterised by the presence of more than one type of movement disorder.[14] Several different subtypes of tardive syndrome exist (panel 1),[15] but we will describe only the most common syndromes.

Orofacial dyskinesias and stereotypies are the most frequently described movements and characterise classical tardive dyskinesia.[16] Orobuccolingual movements are often complex and appear as chewing, jaw deviations, jaw opening or closing, puckering or lip smacking, or abnormal tongue movements often with intermittent tongue protrusions. These movements are often socially disabling and can be associated with difficulties eating, swallowing, speaking, and involuntary self-mutilation from tongue and lip biting.[13] Orofacial movements can be accompanied by involuntary movements of the extremities that are often stereotypical, as well as movements of the neck or trunk that are irregular and unpredictable, consistent with chorea, and occasionally, respiratory dyskinesia.[17]

Tardive dystonia, a less common but more disabling form of tardive syndrome, tends to occur in young men (approximately aged 30 years), as compared with tardive dyskinesia, which mostly occurs in old women (approximately aged 60 years and older), and is manifested as sustained abnormal posturing sometimes with overlying spasms that can be focal (one body region), segmental (contiguous body regions), or generalised.[13] Classic features include retrocollis, opisthotonic posturing, extension of the arms at the elbow, internal rotation at the shoulders, and flexion of the wrists; however, tardive dystonia can be indistinguishable from idiopathic dystonia except for the temporal relationship to use of dopamine receptor blocking agents, and common association with orofacial movements.[17]

Treatment

Vesicular monoamine transporter 2 (VMAT2) inhibitors

The first drugs specifically indicated for the treatment of tardive syndrome were the VMAT2 inhibitors (valbenazine and deutetrabenazine), which were approved in the USA in 2017.[18,19] VMAT2 is a key protein involved in recycling monoamines, dopamine, norepinephrine, and serotonin, following their reuptake into the neuron from the synaptic cleft. VMAT2 shifts monoamines from the cytosol across vesicular membranes and sequesters them into vesicles, allowing for their storage and reutilisation.[20] VMAT2 inhibitors block this packaging of monoamines, which results in rapid degradation of dopamine by monoamine oxidase, leading to depletion of presynaptic dopamine to a degree proportionate to the level of inhibition.[21]

Tetrabenazine, an older VMAT2 inhibitor that was approved for use in hyperkinetic movement disorders in several countries, including the in Canada, France, Germany, Spain, and the UK showed efficacy as a treatment for tardive syndrome, but with only level C evidence based on small randomised and open label trials.[22] Tetrabenazine also has several safety effects, including akathisia and parkinsonism. These side-effects led to the development of valbenazine and deutetrabenazine, both designed to preserve the efficacy of tetrabenazine while improving its safety profile through better pharmacokinetics and the absence of off-target binding.[23] Both drugs have been tested in randomised controlled trials.[22]

Valbenazine is a prodrug of dihydrotetrabenazine linked to a valine molecule, which prolongs its half-life to 20 h allowing for once daily dosing. Phase 2 (KINECT2)[24] and phase 3 (KINECT3)[25] studies for valbenazine were both 6-week, randomised, placebo-controlled, double-blind trials. Patients with tardive syndrome received placebo or escalating doses (up to 75 mg per day) of valbenazine in KINECT2 (n=100), and in KINECT3 (n=225) patients received placebo or valbenazine at 40 mg per day or 80 mg per day. The primary outcome in both studies was the change in the Abnormal Involuntary Movement Scale (AIMS) on randomised videotape segments as rated by a central panel of specialists masked to treatment assignment. Dopamine receptor blocking agents were continued at stable doses throughout the studies. The results showed substantial reduction in the AIMS for the active groups versus the control group in both studies. The responses were dose dependent, with improvements of 2·5 or more points compared with placebo at the highest doses. Most common adverse events reported were headache, sedation, anorexia, akathisia, and urinary tract infection. The patients in KINECT3 were invited to enter a 42-week extension period, followed by a 4-week treatment washout. Patients on active valbenazine continued in the randomised dose group in the double-blind study, and patients on placebo were randomised to either 40 mg per day or 80 mg per day.[26] This study showed evidence of long-term safety and continued reduction in the AIMS score over the 42-week treatment period, with a return to baseline scores following the washout period.

Deutetrabenazine is a VMAT2 inhibitor that replaces hydrogen in tetrabenazine with deuterium, a non-radioactive isotope. Replacement with deuterium results in slower clearance and lower peak concentrations of tetrabenazine, which underlies the drug's increased tolerability and reduced side-effects. The half-life of deutetrabenazine is 9–10 h, allowing for twice daily dosing.[18,20]

Two randomised, placebo-controlled, double-blind studies have tested deutetrabenazine for the treatment of tardive syndrome. The phase 2 ARM-TD study (n=117) randomised patients to placebo or deutetrabenazine up to 24 mg twice daily for 12 weeks.[27] The phase 3 AIM-TD study (n=298) randomised patients to placebo or deutetrabenazine doses of 12 mg per day, 24 mg per day, or 36 mg per day.[28] The primary outcome for both studies was the change in the AIMS severity score from baseline to week 12 rated by a central panel of blinded raters (movement disorder experts) viewing randomised video segments. Both studies showed a substantial reduction of the AIMS of 1·6 points or more for 24 mg per day or higher doses compared with placebo. Adverse events included somnolence and depression, but their frequency was less than 4%. For all VMAT2 inhibitors it is important to be vigilant for depression, parkinsonism, and akathisia.

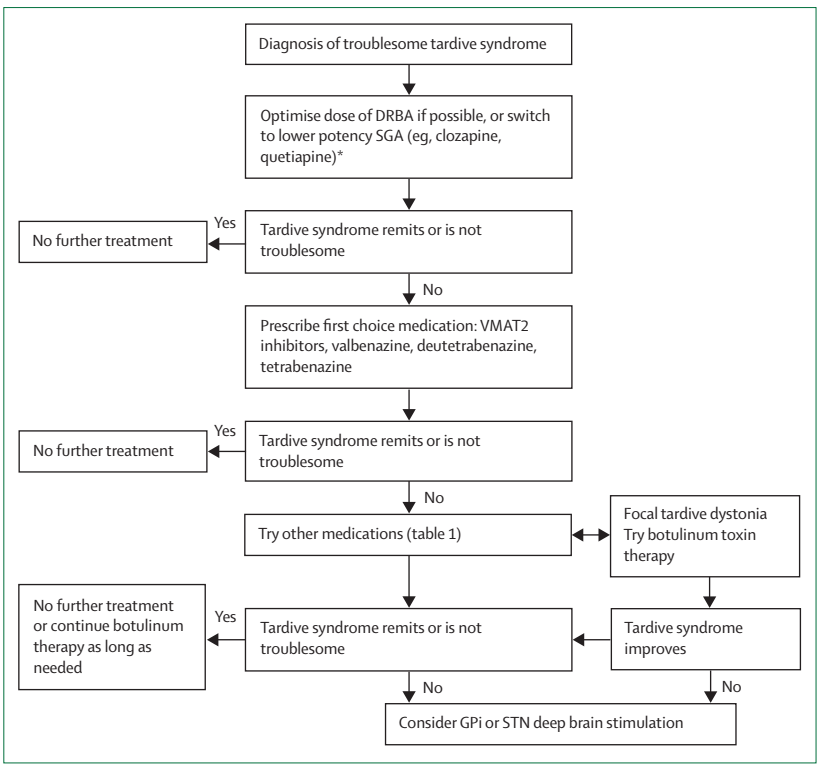

Figure 1: **Algorithm for the treatment of tardive syndrome based on a practical approach not justified by adequate evidence**[4,29,30]

DRBA=dopamine receptor blocking agents. SGA=second and third generation antipsychotics. STN=subthalamic nucleus. VMAT2=vesicular monoamine transporter 2. GPi=globus pallidus interna. *Indicates that tardive syndrome will likely worsen at first before improving.

Following the introduction and approval of these new VMAT2 inhibitors, an evidence-based review of treatments for tardive syndrome was revised, with level A evidence only for valbenazine and deutetrabenazine.[22] When reviewing the pharmacological profiles on the basis of recent studies, valbenazine and deutetrabenazine showed similar suppression of tardive syndrome. The main differences are the longer half-life of valbenazine, which allows once a day dosing, and the increased dosing options for deutetrabenazine, which allow for more precise titration.[21]

None of the VMAT2 treatment trials described the tardive syndrome subtypes of the patients recruited, therefore it is not clear from the publications if these drugs work equally well in all the different tardive movement disorders.

	Mechanism of action	Number of trials (N=total number of patients)	Dose	Common side effects
Clozapine[33]	Low affinity to striatal dopamine D_2 receptors (fast off hypothesis) or $5HT_{2A}$:D_2 blockade ratio (decrease risk of tardive syndromes by decreasing D_2 receptor blockade)	Meta-analysis of 4 open label trials (n=48)	Up to 500 mg per day	Sedation; drooling; agranulocytosis
Amantadine[4,19,22,30,31,]	Weak NMDA receptor antagonist	3 randomised trials (n=44)	100 mg three times a day	Insomnia; constipation; dizziness
Clonazepam[4,22,30,31]	GABAergic-$GABA_A$ receptors (facilitates GABA neurotransmission through $GABA_A$ receptors)	1 randomised trial (n=19)	4·5 mg	Sedation; ataxia
Baclofen[4,19,22, 30,31]	GABAergic-$GABA_B$ receptors (facilitates GABA neurotransmission through $GABA_B$ receptors)	2 randomised trials, 2 open label trials	Up to 120 mg per day	Dizziness; insomnia; nausea; drowsiness
Vitamin B_6 (pyridoxine)[19,22, 30,31]	Antioxidant	2 randomised trials (n=60)	400 mg per day	None
Ginkgo biloba extract EGb-761[4,19,22, 30,31]	Antioxidant	1 randomised trial (n=157)	240 mg per day	None
Levetiracetam[4,19,22, 30,31]	SV2A: inhibition of synaptic vesicle release; N-type calcium channel blockade	1 randomised trial (n=50)	Up to 3000 mg per day	Sedation; nervousness; headache; nasal; congestion
Botulinum toxin (specifically for dystonia)[4,22,31]	Decreased presynaptic cholinergic release	1 single blind observational trial (n=12)	Depends on movement location	Weakness of injected muscles
Deep brain stimulation[4,22,34,35]	Unknown: based on primary dystonia response	2 randomised trials (n=44)	Globus pallidus interna individualised programming	Falls; psychiatric morbidity; equipment-related complications

All treatments listed have been assessed in randomised, controlled, double-blind trials, except for clozapine and botulinum toxin, which have been assessed only in open label trials. SV2A=synaptic vesicle protein 2A. $5HT_{2A}$=5-hydroxytryptamine type 2a.

Table 1: **Potential treatments for tardive syndromes**

Other medical treatments

Although the VMAT2-inhibitors are used as first-line treatment (figure 1), some patients do not respond or experience intolerable adverse effects. Many other drugs have been examined as potential therapies on the basis of various pathogenetic hypotheses, including abnormalities of non-dopaminergic neurotransmitters such as GABA, glutamate, and acetylcholine, as well as those related to oxidative stress. Several recent reviews[4,22,31,32] have covered these drugs in detail. It should be noted that the studies reported with these drugs are generally underpowered, with methodological flaws, and variable results that have not been replicated. Nevertheless, many of these drugs are available and approved for other uses. The switch to clozapine monotherapy is recommended because clozapine has the lowest risk of side-effects of all SGA. Although recent recommendations indicate that there is insufficient evidence,[22] a meta-analysis showed a substantial decrease in tardive syndrome severity after switching to clozapine.[33] The sample size of the meta-analysis was small (n=48) and response was variable, indicating that further study is needed, but it was recommended that moderate to severe tardive syndrome was an indication for making the switch. For tardive dystonia botulinum toxin injections might be another option, but there is also scarce evidence. Nevertheless, in patients with tardive syndrome unresponsive to VMAT2 inhibitors these drugs could represent alternative options (figure 1, table 1).

Surgical treatments

Deep brain stimulation of the globus pallidus interna (GPi-DBS) has been used to treat severe tardive dystonia and dyskinesia refractory to medical therapy. A prospective evaluation of 19 patients receiving GPi-DBS for tardive dystonia and dyskinesia, that included a double-blind evaluation at 6 months after surgery, provided evidence for the effectiveness of the procedure.[34] An average of greater than 50% improvement in AIMS and Extra-pyramidal Symptoms Rating Scale scores were found, and the benefits were sustained as long as 11 years after surgery. Adverse events within 1 year of surgery included falls in five (26%) of 19 individuals, psychiatric morbidity in eight (42%), and equipment-related complications (eg, lead displacement or hardware-related pain) in six (32%). In another randomised, delayed start, double-blind, sham-stimulation controlled trial of GPi-DBS,[35] tardive dystonia and dyskinesia severity was assessed at 3 months (blinded phase) and 6 months (open extension phase) in 25 patients. The primary endpoint was the percent change in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) between active versus sham

stimulation using blinded-video assessments. The pre-specified sample size was not met, hence the study was underpowered. There was no group difference at month 3 (23% *vs* 12% change) for the BFMDRS but there was a substantial difference in AIMS scores. At 6 months of stimulation, a combined 42% improvement in both groups was observed along with substantial improvement in quality of life. Adverse events related mainly to surgical implantation of the DBS device, which were all reversed.

The relative efficacy of GPi-DBS for improving tardive dystonia of different body parts and the temporal course of improvement was assessed in eight patients.[36] Although improvements were seen in all body parts, the time course of response varied from a few weeks to months and tended to be slower in the neck and trunk.

There is less experience with DBS of the subthalamic nucleus for treating tardive syndrome. A retrospective evaluation of ten patients receiving DBS in the subthalamic nucleus found improvements of over 50% in the BFMDRS and AIMS at 1 week after surgery.[37] With continued follow-up, mean improvements increased to over 80% and were sustained for the mean of 65 months.

The published literature suggests possible efficacy of GPi-DBS for tardive dystonia with a reasonable safety profile. Surgical treatments should be used only for those with intolerable movements that are unresponsive to medical therapy, and done in centres with experienced clinicians (figure 1). Controlled studies with assessors blinded to the intervention are needed to increase the quality of evidence.

Drug-induced parkinsonism

Epidemiology

Drug-induced parkinsonism is common and represents the most serious iatrogenic movement disorder in older people (aged >50 years), as it increases the risk of gait dysfunction, falls, and nursing home placement.[38] It typically occurs in patients treated with dopamine receptor blocking agents and less frequently with other drugs. In two studies from the USA[39] and Europe,[40] the frequency of drug-induced parkinsonism, among all forms of parkinsonism, was found to be relatively consistent, ranging from 8% to 12%, with an overall incidence of 2·5–3·3 per 100 000 person per year. Drug-induced parkinsonism is more common in women and its frequency increases with age. The incidence of drug-induced parkinsonism decreased by 68% between 1976 and 2005,[39] probably because of the increasing use of SGA. A meta-analysis of studies in patients with schizophrenia and related psychoses treated with 12 different FGA and SGA[41] showed that drug-induced parkinsonism occurred in 2% of patients treated with asenapine and in 29% of patients treated with sulipride. As a consequence of the small number of studies available and large confidence intervals, the only SGA yielding substantially smaller prevalence rates than chlorpromazine (21%) and haloperidol (23%) were clozapine (4%), aripiprazole (7%) and olanzapine (8%).

***Panel 2:* Dopamine transporter (DaT)-SPECT and the diagnosis of drug-induced parkinsonism**

1. Signs and symptoms of drug-induced parkinsonism and Parkinson's disease can be identical. Neither motor nor non-motor symptoms help in distinguishing drug-induced parkinsonism from Parkinson's disease. Features that could suggest drug-induced parkinsonism include:
   - Subacute onset
   - Absence of tremor
   - Symmetric signs at onset
   - Presence of tardive syndrome
   - Absence of hyposmia
   - Absence of sleep disorders and urinary symptoms
   - Two or fewer cardinal features of Parkinson's disease
2. ^{123}I-Ioflupane was approved by the European Medicines Agency as DaTSCAN in 2000 and by the US Food and Drug Administration in 2011 for clinical use to differentiate essential tremor from conditions associated with presynaptic dopaminergic dysfunction
3. DaT-SPECT measures functional integrity of the dopaminergic nigrostriatal pathway; this technique can differentiate, with a high sensitivity and specificity (up to 85%), patients with Parkinson's disease from those with drug-induced parkinsonism
4. When DaT-SPECT is normal in a patient on dopamine receptor blocking agents, parkinsonism is caused by neuroleptic-induced D_2-receptor blockade (pure drug-induced parkinsonism).
5. Several drugs, particularly stimulants and antidepressants, can alter DaT binding and make the scan difficult to interpret

Therefore, the SGA, although not risk free, appear to carry a risk for drug-induced parkinsonism that is about half of that of FGA. Although decreasing, there is a general consensus among clinicians that drug-induced parkinsonism is underestimated and, despite the greater use of SGA, remains a common cause of parkinsonism, especially in people with psychiatric disorders or dementia

Clinical features

Drug-induced parkinsonism develops subacutely over days to months, most commonly when the drug is started or when the dose is increased. It may even develop in patients who have been on dopamine receptor blocking agents for decades, because of the development of actual Parkinson's disease or the increased susceptibility to drug-induced parkinsonism of the ageing brain. Drug-induced parkinsonism can take several months, or even years to resolve after the inciting drug is stopped. There are no differences in the features of parkinsonism between FGA and SGA[42] and there are no clinical characteristics that can reliably distinguish drug-induced parkinsonism from Parkinson's disease, or drug-induced parkinsonism from antipsychotic exacerbated Parkinson's disease. This

Panel 3: A case study of drug-induced parkinsonism versus Parkinson's disease

A 71-year-old man presented to a neurology clinic with a possible diagnosis of Parkinson's disease. It first started as a right hand tremor several years earlier and had recently spread to the left hand. His tremor progressed very slowly over time and he was initially thought to have Parkinson's disease. At the time of presentation, the tremor was reported by his wife as present constantly. In the last year, he noted a shuffling gait and in the last 3 months had two falls backwards. He also had start hesitation. He reported micrographia and trouble with buttons and shaving because of the tremor. He had a history of anxiety and bipolar disorder from age 50 years. For his bipolar disorder he was treated with aripiprazole 10 mg per day and olanzapine 2·5 mg per day. MRI scan showed age-related atrophy and small white matter microvascular lesions. On neurological exam he had moderate rest tremor of the hands bilaterally, moderate neck and mild limb rigidity, and mild bradykinesia. His gait was normal except for decreased arm swing and a stooped posture. There was no retropulsion or freezing. A dopamine transporter (DaT)-SPECT was done and the results were normal. We gave him the options to continue with his usual prescription of antipsychotics if the tremor was not troublesome; or if troublesome, to treat the tremor with amantadine or carbidopa/levodopa, or lower or stop the antipsychotics. His psychiatrist decreased the aripiprazole to 5 mg per day and his symptoms improved but remained present. He has been followed up for 6 years with no change in motor symptoms.

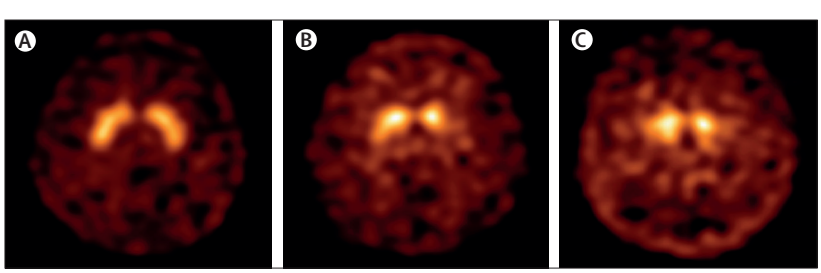

Figure 2: **Dopamine transporter (DaT)-SPECT findings in one patient with pure drug-induced parkinsonism and in two patients with Parkinson's disease**
Nigrostriatal DaT binding is normal in patients with drug-induced parkinsonism (A), whereas it is asymmetrically (B) or symmetrically (C) reduced at the putaminal region in patients with Parkinson's disease.

is the area for which dopamine transporter (DaT)-SPECT has proven to be promising (panel 2).

A proper diagnosis of drug-induced parkinsonism or Parkinson's disease is crucial in terms of management and prognosis (panel 3). SPECT imaging using ligands of the pre-synaptic DaT, such as ^{123}I-Ioflupane (^{123}I-FP-CIT-SPECT), allows the study of the functional integrity of the dopaminergic nigrostriatal pathway.[43]

Many drugs, particularly dopaminergic CNS stimulants (cocaine, amphetamine-related compounds, methylphenidate, and modafinil), can substantially interfere with DaT binding, making DaT-SPECT difficult to interpret. Therefore, they need to be stopped before the scan. Additionally, many aminergic medications (sertraline, citalopram, imipramine, and duloxetine) can also interfere with the DaT imaging interpretation, but with minor effects.[44]

Several studies[43,45] have shown that DaT-SPECT can distinguish between patients with drug-induced parkinsonism and Parkinson's disease with a high sensitivity and specificity (up to 85%). Moreover, DaT-SPECT results lead to practical changes in patient management and the outcomes of these changes are consistent with scan results.[45] Drug-induced parkinsonism is considered a form of postsynaptic parkinsonism due to D_2-receptor blockade and therefore SPECT is expected to be normal in these patients (pure drug-induced parkinsonism).[44]

DaT imaging studies have shown that some patients with presumed drug-induced parkinsonism can show subtle or severe dysfunction of the presynaptic nigrostriatal dopaminergic pathway. These patients tend to develop parkinsonism in a shorter timeframe than those with normal scans (<6 months) and can have only partial recovery when the inciting drug is discontinued.[46] DaT binding can be severely reduced in up to 55% of patients with drug-induced parkinsonism,[45,47,48] suggesting that these patients have Parkinson's disease or a subclinical form of the disease that is unmasked by dopamine receptor blocking agents treatment (figure 2). Although there is a scarcity of neuropathological data confirming that patients with both drug-induced parkinsonism and abnormal DaT binding have Lewy body diseases, autopsy studies[49] have shown that some cases had neuropathological features consistent with preclinical Parkinson's disease.

Therefore, DaT-SPECT can be useful in determining whether patients with drug-induced parkinsonism have underlying Parkinson's disease. In patients with an abnormal DaT-SPECT, olfactory function is reduced,[50] the disease progresses over time (measured clinically),[51] they showed more than two cardinal features of parkinsonism,[45] and they benefit from levodopa therapy.[51,52]

Treatment

Drug-induced parkinsonism can be severely disabling. The first recommendation is to withdraw or reduce the dopamine receptor blocking agents (if possible) and monitor the patient for a period of at least 6 months. If the patients psychiatric condition worsens, switching to a drug with a lower affinity to D_2 receptors is suggested. Only quetiapine and clozapine have been shown not to worsen parkinsonism.[53]

Pharmacological treatment of drug-induced parkinsonism has not been well studied. Anticholinergic drugs (including trihexyphenidyl, benztropine, and diphenhydramine) are often used based on anecdotal evidence and previous small trials. There is similarly poor evidence to support amantadine.[54] Often these drugs are not well tolerated. Levodopa is not often used in drug-induced

parkinsonism because of the postsynaptic D_2-receptor blockade of antipsychotics and potential worsening of psychosis. However, in patients with both drug-induced parkinsonism and abnormal DaT-SPECT (and less frequently in patients with pure drug-induced parkinsonism) parkinsonian symptoms can improve on levodopa, with a magnitude of response comparable to that observed in patients with Parkinson's disease (improvement in UPDRS-III score >30%), and with few psychiatric side-effects.[45,51]

Acute dystonic reactions

Acute dystonic reactions observed with dopamine receptor blocking agents are more frequent when FGA are used (17% of patients treated with haloperidol) than when SGA are used (<2% for quetiapine and clozapine treated individuals).[41] They are also observed with antiemetics and promotility drugs. Acute dystonic reactions are more common in young men and in boys and infants[55] and develop rapidly after drug dosing (ie, initial treatment or increasing dose), even after a single dose. The clinical features include oculogyric-like crisis, blepharospasm, cervical and truncal dystonia, oromandibular dystonia, and acute laryngeal-pharyngeal dystonia. The dystonia can be focal, segmental, or generalised. If severe, the result could be impairment of speech, swallowing and breathing, and potentially leading to severe and sometimes life-threatening complications, including subluxation of joints and aspiration.

Equally dramatic and rapid is the response of acute dystonic reactions to anticholinergic drugs (diphenhydramine or benztropine) when given intravenously or intramuscularly, producing relief within minutes.[55] Acute dystonic reactions can recur some hours after the first anticholinergic injection and hence can require repeated administration followed by several days of oral therapy. When identified, the generally agreed upon treatment can be to discontinue or switch the inciting drug; however, anticholinergics can be used prophylactically instead. Pathogenic mechanisms underlying acute dystonic reactions are unclear and no plausible hypotheses have been proposed.

Acute and subacute akathisia

Akathisia is defined as a sensation of restlessness, sometimes perceived as anxiety. Patients may feel an associated tension, irritability, and show aggressiveness, potentially leading to self-harm. Stereotyped movements occur, including pacing, marching in place, shifting weight when standing, rubbing their hands, patting their thighs, rocking in place while seated, which provide limited alleviation of the subjective features.[56] Acute akathisia can begin within hours to days after initiating treatment with dopamine receptor blocking agents and can occur in 50% of patients within 1 month.[57] When severe, it is extremely dysphoric and can cause paradoxical worsening of psychosis shortly after antipsychotic drug initiation. It is important to understand that acute akathisia and tardive akathisia, a problem associated with long-term use of dopamine receptor blocking agents, are phenomenologically identical, but opposites in their response to drug treatment. Acute akathisia improves when removing the antipsychotic and tardive akathisia worsens.

In a chart review[58] of 592 patients with cancer seen over a 3-year period, 30 (5%) were diagnosed with antiemetic induced akathisia, generally taking 4–6 months for the diagnosis to be made. In a study[59] of patients with schizophrenia living in the community, the prevalence of akathisia was 19%. There are notable differences in the annual incidence of akathisia depending on the drug used: 4% from quetiapine or olanzapine, 20% with other SGA, and 50% with haloperidol. Reported rates of akathisia are higher with asenapine, aripiprazole, and lurasidone than with other SGA.[60]

The generally agreed upon approach to therapy based on consensus is recognition followed by a discontinuation, lowering, or switching the inciting drug. There have been no recent multicentre trials to guide treatment; however, evidence from randomised double blind and open label trials suggests that propranolol, 5-hydroxytryptamine antagonists (mianserin, mirtazapine, and trazodone), vitamin B6, and benzodiazepines might be helpful.[61]

Movement disorders due to other drugs

Drug-Induced Parkinsonism

Lithium has been identified as a cause of parkinsonism in several reports: in some cases lithium levels were supratherapeutic,[62] whereas in others they were therapeutic.[63] In a study[45] of 55 possible drug-induced parkinsonism cases, lithium was the suspect cause in nine (15%) and DaT-SPECT was normal in eight (89%).

Epidemiological evidence supporting the likelihood of an association between lithium and parkinsonism is provided by a retrospective cohort study[64] using healthcare administrative databases in Ontario, Canada. In over 1700 patients aged 65 years and older with no previous antipsychotic use, lithium monotherapy for at least 1 year was associated with an increased incidence of subsequent dopaminergic drug prescribing (adjusted hazard ratio: 1·87, 95% CI 1·06–3·30) compared with antidepressant users.

Valproate is an antiepileptic also used as a mood stabiliser and for migraine prophylaxis. A report[65] found that 9 (8%) of 118 consecutive patients treated with the drug had resting tremor. The mean duration of parkinsonian signs after valproate withdrawal was reported to be 4·5 months, varying from a few days to 2 years.[66] Further, some patients were levodopa responsive with levodopa-induced dyskinesia.[67]

Cinnarizine, a selective T-type calcium channel blocker (receptors highly expressed in the basal ganglia) used for vertigo and motion sickness, and its derivative flunarizine, used for migraine prevention, have been associated with drug-induced parkinsonism. The risk can be twice as high

	Neuroleptic malignant syndrome[79,57,80]	Serotonin syndrome[80,81,82]	Parkinsonism hyperpyrexia disorder[80,83]
Cause	All DRBA; dopamine depleting drugs	Overdose or administration of single or multiple serotonergic agents; antidepressants; some opioids; triptans; methylene blue; linezolid; St John's wort; Illicit substances (eg, MDMA and cathinones)	Withdrawal of dopaminergic therapy; loss of deep brain stimulation
Core clinical features	Hyperthermia; rigidity, tremor; autonomic dysfunction; mental status change	Hyperthermia; myoclonus, rigidity; autonomic dysfunction; mental status change; gastrointestinal symptoms	Hyperthermia; rigidity, tremor; autonomic dysfunction; mental status change
Frequency	FGA: 0·2%; SGA: 0·006%	0·07–0·09% among patients receiving serotonergic drugs	0·3–3·6% of patients with PD
Mortality rate	FGA: 10–20%; SGA: 5·5%	5%	15%
Risk factors	Higher doses or multiple antipsychotics; male sex; young adults; agitation; confusion; catatonia; dehydration; previous NMS episodes; ethnic origin; developmental disorder in children	High doses of one or multiple serotonergic drugs	Advanced PD; higher daily levodopa doses increase risk; motor fluctuations; psychosis; dehydration; before PHS episodes
Treatment	Recognition; cessation of triggering drugs; supportive care; dopaminergic drugs; benzodiazepines; dantrolene; ECT	Recognition; cessation of triggering agent; supportive care; serotonergic antagonists; benzodiazepines; dantrolene	Recognition; rapid reintroduction of dopaminergic treatment; re-implantation of deep brain stimulation; supportive care

DRBA=dopamine receptor blocking agents. MDMA=3,4-methylenedioxymethamphetamine. FGA=first generation antipsychotics. SGA=second and third generation antipsychotics. PD=Parkison's disease. NMS=neuroleptic malignant syndrome. PHS=parkinsonism hyperpyrexia syndrome. ECT=electroconvulsive therapy.

Table 2: **Drug-induced movement disorder emergencies**

for flunarizine compared with cinnarizine. The prevalence of parkinsonism with these drugs was found in 280 (3%) of 9830 patients in a population-based study in Taiwan.[68]

There are many additional drugs reported to be associated with the development of parkinsonism in case reports and case series.[69] The most common classes of drugs reported in a pharmacovigilance study[69] from France are antidepressants and antihistamines. A causal relationship is difficult to establish with certainty, but the resolution of parkinsonism after withdrawal of the suspect drug is supportive, and was reported in 137 (88.7%) of the 155 cases.

Drug induced non-parkinsonian tremor

Drug-induced tremor refers to an action (postural and kinetic) tremor that is caused by using various medications at the same time (ie, a consequence of their interaction). It typically represents an enhanced physiological tremor, which is a bilateral upper limb action tremor with low-amplitude, high-frequency oscillations, mediated by both central (8–12 Hz component) and peripheral (segmental stretch reflex) mechanisms.[70] The most common medications from different classes causing drug-induced tremor and possible mechanisms are listed in the appendix.[71] According to the new classification, drug-induced tremors usually manifests as an isolated tremor syndrome or sometimes combined with other systemic or neurological signs and should be differentiated from other tremor syndromes, including essential tremor and Parkinson's disease.[72] Features in the clinical history, tremor characteristics, associated signs and laboratory tests are important in the differential diagnosis. More specifically, factors highly suggestive of drug-induced tremor are: a temporal relationship between starting medication and the occurrence of tremor; a dose-response relationship; exclusion of other medical causes of tremor (eg, hyperthyroidism, hypoglycaemia); and an absence of tremor progression. Other factors that could contribute to the tremor are polypharmacy in the elderly, metabolic disorders, anxiety and mood states, withdrawal from ethanol, fever, and shivering because of low temperature.[73] It should also be noted that sometimes essential tremor or Parkinson's disease can be unmasked by these drugs.

Two widely used medications, lithium and valproate, are best known for their association with enhanced physiological tremor. Tremor induced by lithium is among the most frequent drug-induced tremor occurring in about 30% of treated patients.[71] It often occurs in older patients and it is more common in men than in women. Tremor is mild and not disabling in most patients; however, about a third of patients find it troublesome. It can improve over time with continuing therapy and can be increased by concomitant drugs such as selective serotonin-reuptake inhibitors, tricyclic antidepressants, or valproate. Tremor improves when stopping or reducing the dose of lithium.[74]

Up to 80% of patients treated with valproate develop tremor, but only 25% complain about it, and patients requiring treatment are commonly older women.[65] Valproate-induced tremor appears to be dose related and improves with dose reduction. Tremor amplitude seems to be higher with immediate release versus controlled-release preparations, probably because of a greater peak-to-trough variation in drug levels.[75] The mechanisms for lithium and valproate-induced tremor are unknown.

Several factors should be considered before treating these tremors. In most patients, tremor is not disabling and improves over time. Concomitant drugs or substances can worsen tremor (eg, caffeine and antiepileptics). Dose reduction itself often improves tremor without worsening the psychiatric disease. If treatment is needed, propranolol is the most commonly prescribed and effective drug.[74]

Other movement disorders

Apart from drug-induced parkinsonism and drug-induced tremor, several non-dopamine receptor blocking agents can rarely cause other reversible dyskinesias such as orofacial stereotypies, tics, acute dystonic reactions, akathisia, and choreoathetosis, which should be included in the differential diagnosis (appendix)[76–79] These adverse events are clinically similar to those reported with

See Online for appendix

dopamine receptor blocking agents and respond equally well to discontinuation of the causal drug. However, persistent dyskinesias due to non-dopamine receptor blocking agents are rare and remain controversial.[16] Because descriptions of movement disorders associated with non-dopamine receptor blocking agents are mostly from case reports complicated by polypharmacy, the causality of these remains unclear.

Drug-induced movement disorder emergencies

There are three major forms of drug-induced movement disorders with systemic manifestations that are life-threatening neurological emergencies. They are acute in onset and share core clinical features affecting mental status, motor symptoms, and autonomic and thermoregulatory functions (table 2).[57] Neuroleptic malignant syndrome occurs secondary to the initiation or increased dose of dopamine receptor blocking agent. The incidence and mortality of neuroleptic malignant syndrome could be diminished with the introduction of SGA. This syndrome remains primarily a clinical diagnosis and validated standardised diagnostic criteria have been developed.[79] Although serum creatine kinase elevations are common, they are non-specific and not pathognomonic.[84] Reports highlight difficulties distinguishing neuroleptic malignant syndrome from NMDA-receptor encephalitis.[85]

Parkinsonism hyperpyrexia syndrome occurs following the abrupt reduction of dopaminergic medication in Parkinson's disease and related disorders.[86] Parkinsonism hyperpyrexia syndrome is reported in the context of non-compliance with dopaminergic medications, the development of severe so-called off periods, concurrent illnesses, dysphagia, abrupt changes in medications, diet or enteral feedings, and withholding medication before operations.[87,88] The syndrome can also emerge in patients treated with DBS, related to reduction of dopaminergic drugs or loss of DBS stimulation (battery failure and explantation).[86]

Serotonin syndrome results from toxicity of single or combined serotonergic drugs.[81,89] Diagnostic criteria have been proposed and include behavioral, autonomic, neuromuscular, and gastrointestinal symptoms.[81,89] Presentations reflect a continuum of dose-dependent toxicity ranging from transient agitated delirium to a full-blown hyperthermic crisis indistinguishable from neuroleptic malignant syndrome. Severe cases are associated with monoamine oxidase inhibitors, including drugs used in medical or surgical settings (linezolid and methylene blue) and herbal products (St John's wort) that have clandestine monoamine oxidase inhibitor activity.

Conclusion

There is strong evidence that, although new antipsychotics appear to carry reduced risk, drug-induced movement disorders are still common because of the increased prescribing practices. As such, drug-induced movement disorders still represent an important clinical issue and better education, awareness, and vigilance are required for prompt diagnosis.

The development of valbenazine and deutetrabenazine offer new safe and effective treatments for tardive syndromes. However, approval in the USA, but not in other countries, and the high costs limit accessibility and affordability. The effect of these drugs on subtypes of tardive syndromes also needs to be studied. GPi-DBS is potentially safe and effective in the treatment of severe, pharmaco-resistant tardive dystonia, but larger controlled trials are needed to gather more evidence.

DaT-SPECT is useful for diagnosing concomitant neurodegenerative parkinsonism in patients treated with dopamine receptor blocking agent, but it is not yet approved for this purpose. DaT-SPECT might further help to identify patients at risk of progression and possibly predict the response to levodopa. Future large randomised, placebo-controlled trials of levodopa in drug-induced parkinsonism are needed.

Other drugs that can cause a broad array of movement disorders are still in widespread use. Hopefully, the development and testing of drugs with reduced liability for drug-induced movement disorders, including new antipsychotics, will add to the clinical armamentarium over the next 5 years.

In the clinical setting, medications, including those recently discontinued, have to be considered in the evaluation and treatment of patients presenting with movement disorders. Some disorders are entirely due to medication, even at non-toxic doses, whereas others such as Parkinson's disease are altered by them, sometimes confounding the diagnosis.

Search strategy and selection criteria

We searched PubMed and Embase for articles published in peer-reviewed journals in any language from July 1, 2013, to January, 2019, with the following terms: "Drug-induced movement disorder", "tardive dyskinesia", "drug-induced parkinsonism", "akathisia", "acute dystonia", "neuroleptic malignant syndrome", "parkinsonism hyperpyrexia syndrome", "serotonin syndrome", "dyskinesia hyperpyrexia syndrome", and "drug-induced tremor". We also searched the reference lists of selected review papers. The final reference list was generated on the basis of relevance to this Review and novelty.

Contributors

This work is solely the work of the authors. All authors contributed equally to the writing of the first draft and editing the final draft of the manuscript.

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