Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

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To cite this article: Dénes Zádori, Gábor Veres, Levente Szalárdy, Péter Klivényi & László Vécsei (2015) Drug-induced movement disorders, Expert Opinion on Drug Safety, 14:6, 877-890, DOI: 10.1517/14740338.2015.1032244

To link to this article: https://doi.org/10.1517/14740338.2015.1032244

Published online: 16 May 2015.

EXPERT OPINION

Drug-induced movement disorders

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Introduction: Drug-induced movement disorders (DIMDs) can be elicited by several kinds of pharmaceutical agents. The major groups of offending drugs include antidepressants, antipsychotics, antiepileptics, antimicrobials, antiarrhythmics, mood stabilisers and gastrointestinal drugs among others.

Areas covered: This paper reviews literature covering each movement disorder induced by commercially available pharmaceuticals. Considering the magnitude of the topic, only the most prominent examples of offending agents were reported in each paragraph paying a special attention to the brief description of the pathomechanism and therapeutic options if available.

Expert opinion: As the treatment of some DIMDs is quite challenging, a preventive approach is preferable. Accordingly, the use of the offending agents should be strictly limited to appropriate indications and they should be applied in as low doses and as short duration as the patient's condition allows. As most of DIMDs are related to an unspecific adverse action of medications in the basal ganglia and the cerebellum, future research should focus on better characterisation of the neurochemical profile of the affected functional systems, in addition to the development of drugs with higher selectivity and better side-effect profile.

Keywords: basal ganglia, drug-induced side-effects, movement disorders, tardive syndromes

Expert Opin. Drug Saf. (2015) 14(6):877-890

1. Introduction

Drug-induced movement disorders (DIMDs) can be caused by several kinds of agents and almost all sorts of movement disorders can occur as a result of medication side effect (**Table 1**; [1,2]). The underlying pathomechanism is only known in a subset of DIMDs; however, an altered neurotransmission in the basal ganglia (predominantly in the striatum; **Figure 1**) and the cerebellum is presumed to play a role. Based on the onset of symptoms, DIMDs can be classified as acute (occurring within hours to days), subacute (occurring after days to weeks) or chronic (occurring after months spent in the exposure of the offending drug). Following the initial presentation of tardive syndromes, which represent the most challenging conditions among DIMDs, the current review focuses on the concise delineation of each movement disorder induced by pharmaceuticals as well as on the discussion of potential therapeutic options. The description of laboratory chemicals, illicit drugs or recreational substances able to induce movement disorders is out of the scope of this paper.

2. Methods

The aim of the authors was to present a literature review as defined by Grant and Booth [3] on the field of DIMDs.

informa healthcare

10.1517/14740338.2015.1032244 © 2015 Informa UK, Ltd. ISSN 1474-0338, e-ISSN 1744-764X

Article highlights

- Most of drug-induced movement disorders (DIMDs) are related to an unspecific adverse action of the offending agents in the basal ganglia and the cerebellum; therefore, better characterisation of the neurochemical profile of the affected functional systems is one of the most important cues for future research.
- DIMDs are frequently overlooked by the clinical community, leading to a general increase in the incidence of these mostly reversible conditions; therefore, high-quality education is essential to achieve early recognition.
- The most important factor in the management of DIMDs is prevention: that is, the offending agents should be administered for as short duration and in as low doses as the patient's condition allows.
- In case the withdrawal of the offending drug is insufficient to provide proper symptomatic relief, certain pharmaceuticals may play special roles in the amelioration of DIMDs.
- Tardive syndromes, which can also occur following dose reduction or a sudden withdrawal of the offending drug, represent the highest therapeutic challenge.

This box summarises key points contained in the article.

2.1 Search strategy

PubMed (MEDLINE) and Web of Science (1966 to December 2014) were used as search engines for relevant articles. The key terms of search in the first step included 'drug-induced' *and* 'movement disorders' or 'Parkinsonism' or 'tremor' or 'chorea' or 'dystonia' or 'ataxia' or 'myoclonus' or 'tic' or 'akathisia' or 'stereotypy' or 'restless legs syndrome' or 'periodic limb movements of sleep' or 'rapid eye movement sleep behaviour disorder' or 'myokimia' or 'myorhythmia' OR 'tardive syndromes' or 'neuroleptic malignant syndrome' or 'serotonine syndrome' *and* 'review'.

The key terms of search in the second step included 'basal ganglia' or 'striatum' *and* 'neurochemistry' or 'neurotransmission' *and* 'glutamate' or 'GABA' or 'acetylcholine' or 'dopamine' or 'serotonine' or 'noradrenaline' or 'histamine' or 'opioid'.

2.2 Appraisal

If reviews were available, the most comprehensive ones have been selected for further thorough assessment for each type of movement disorders or group of movement disorders (e.g., hypokinetic or hyperkinetic). Thereafter, all groups of offending agents, including commercially available medicines and excluding laboratory chemicals, illicit drugs or recreational substances, have been collected. In the next step, based on the collected information, a search for relevant occurrences of agents (randomised controlled trials, cohort studies, case series or single case reports) in all groups of medicines has been conducted for each type of movement disorders. If there was not any available occurrence, the problematic group of medicines was excluded from the list for the respective type of movement disorder.

With regard to the second step of searches, the studied neurochemical inputs and the respective receptors have been collected for all major types of striatal neurons.

2.3 Synthesis

After collecting all the necessary information, the synthesis of the available data from the literature was provided for each group of movement disorders in a narrative style, including the pathomechanism and therapeutic options, if available.

With regard to the neurochemistry of the striatum, a demonstrative figure is provided.

2.4 Analysis

An expert opinion section is provided for analytic purposes.

3. Drug-induced movement disorders

3.1 On the significance of tardive syndromes

Among chronic DIMDs, tardive dyskinesias (TDs) represent a rather specific subgroup [4,5]. TDs represent a group of antipsychotic-induced delayed-onset iatrogenic movement disorders, which can manifest in stereotypy, dystonia, akathisia, tic, tremor, myoclonus, chorea, Parkinsonism and withdrawal emergent syndrome. Furthermore, in some cases, sensory symptoms such as paresthesia, pain and an inner urge to move can also accompany the movement disorders. The term 'classic TD' was introduced to describe the prototypical oro-bucco-lingual stereotypic movements [4]. In addition to the exposure to antipsychotics (a duration- and dose-related effect [6]), older age [7], African-American ethnicity [8], the presence of diabetes mellitus [9] and the occurrence of acute dystonic reactions (ADRs) or Parkinsonism [6] may be the major predisposing risk factors for the development of TD. Even third-generation antipsychotics (e.g., aripiprazole [10]) have the potency to evoke TD. The proposed pathomechanisms of TD include dopamine 2 receptor upregulation with subsequent hypersensitivity, GABA insufficiency, increased endogenous opioid effect, glutamate excitotoxicity, oxidative stress and genetic susceptibility as well [4,5]. In addition to antipsychotics, antidepressants (e.g., duloxetine [11]), anti-Parkinsonians (e.g., levodopa [12]), mood stabilisers (e.g., lithium [13]) and calcium channel blockers (e.g., flunarizine [14]) can also induce tardive syndromes. The prevalence of antipsychotic-induced TD is relatively high, reaching ~ 20% [15]. In addition to the development of TD while the patients are on medication, the condition can also occur following dose reduction or a sudden withdrawal of the applied antipsychotic drug [16]. The special importance of the distinction of TD from other DIMDs, especially from those with relatively rapid onset, is based on therapeutic considerations. In most cases of TD, in contrary to acute- or subacute-onset DIMDs, clinicians face therapeutic challenges. In a considerable number of cases,

Table 1. The list of pharmacological classes of drugs with the potency of inducing movement disorders.

Group	DIA	DIM	DIT	DID	DIC	DIP	Akathisia	RLS	SS	DITic	NMS	RBD RSWA	Myokimia	PLMS	Myorh
Antidepressants	±	+++	+++	++	+	+	+	+++	++	±		++		++	
Antipsychotics		++	±	++	±	+++	+++	+		++	+++				
Anti-epileptics	+++	++	+	+	++	±		+	±	+					
Antimicrobials	+++	+++	±	±		±							±		
Anti-arrhythmics	+++	+	++		±	+						±			
Mood stabilisers	+++		++		+	±		±	±						
Anti-emetics		±	±	++		±	+++				±				
Opioids		+++		±	±			±	++						
Antiparkinsons		+++		±	++			±				±			
Immunosuppressants	+++		+++			±									
Chemotherapeutics	+++	+	+	±									±		
Benzodiazepines	+++	+		+											
Ca^{2+}-channel blockers		+		+		++							±		
Psychostimulants			±	+	+		±			+					
Hormones	±		++		+			++							
Bronchodilators			+++												
Anaesthetics	±	±		±	±										
Anticholinergics				±	+	±									
VMAT inhibitors			+			±									
Antihyperlipidemics	±					±							±		
Antihistamines				+	±										
Central muscle relaxants	±				±										
AChE inhibitors		±		±											
H_2 receptor blockers				±				±							
Antirheumatics					±								±		
NSAIDs		±		±											
Sleeping pills	±														
INFα2A inhibitors															±
Antimetabolites					±										
DA synthesis blockers						±									

We applied the following scoring system: ±: only 1 – 2 case reports/case series; +: 3 – 10 case reports/case series; ++: 10 – 20 case reports/case series or at least one cohort study/randomised control trial/systematic review; +++: more than 30 published case reports/case series or at least two cohort studies/randomised control trials/systematic reviews.

AChE: Acetylcholinesterase; Ca^{2+}: Calcium; DA: Dopamine; DIA: Drug-induced ataxia; DIC: Drug-induced chorea; DID: Drug-induced dystonia; DIM: Drug-induced myoclonus; DIP: Drug-induced Parkinsonism; DIT: Drug-induced tremor; DITic: Drug-induced tic; H_2: Histamine-2 receptor; Myorh: Myorhythmia; NMS: Neuroleptic malignant syndrome; PLMS: Periodic limb movements of sleep; RBD: Rapid eye movement (REM) behavior disorder; RLS: Restless legs syndrome; RSWA: REM sleep without atonia; SS: Serotonin syndrome; VMAT: Vesicular monoamine transporter.

the beneficial effect of dose-reduction or switching to a medication with better side-effect profile is questionable and the treatment armory is limited as well. First of all, the preventive approach is preferable: physicians should be very cautious with the prescription of antipsychotics and they ought to be used when they are strictly indicated and only for as short period as possible and in as low doses as the condition allows [17]. In general, with regard to the limited therapeutic options in TD, mostly vesicular monoamine transporter (VMAT) inhibitors (e.g., tetrabenazine [18]) amantadine [19], benzodiazepines (e.g., clonazepam [19]), anticholinergics (e.g., trihexyphenidyl [20]), β-blockers (e.g., propranolol [21]), anti-epileptics (e.g., levetiracetam [22]), chemodenervation with botulinum toxin injections [23] or deep brain stimulation [24,25] may come into account. Although there are reports indicating the beneficial effects of clozapine in the treatment of TD [26], the available data are rather inconclusive [27], and therefore, an evidence-based recommendation cannot be established.

3.2 Drug-induced Parkinsonism

Probably the most important criterion of drug-induced Parkinsonism (DIP) is the absence of history of Parkinsonism before the administration of the offending drug [28]. Therefore, the exclusion of idiopathic Parkinson's disease (iPD [29]) in the differential diagnostic workup of DIP (the second most common cause of Parkinsonism after iPD [30]) is essential. Fortunately, there are some valuable tools for this workup [31]. With regard to clinical phenomenology, the development of symptoms within 3 months, the symmetrical presentation of symptoms, the relative absence of resting tremor, the coexistence of oromandibular dyskinesias and poor or absent response to levodopa all favour the diagnosis of DIP [28,32]. Although the formal indication of

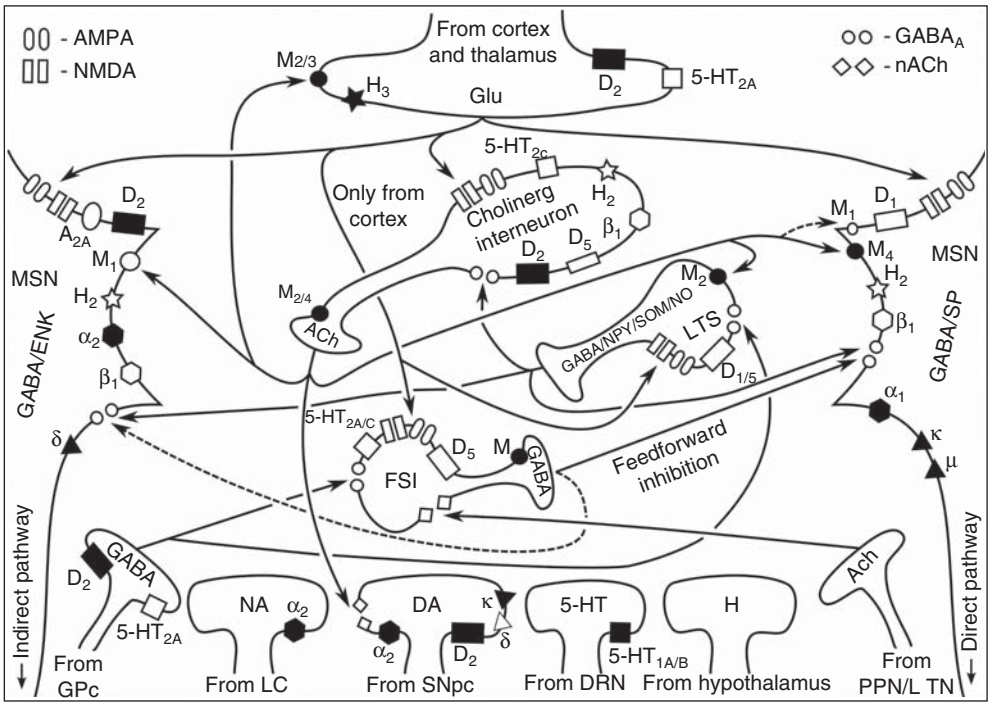

Figure 1. The schematic depiction of the neurochemical aspects of striatal architecture. The black plain figures represent inhibition, whereas white plain figures excitation; the reduced size of plain figures or dashed arrows represent the subdominant effect; the arrows represent synaptic connections, whereas boutons without arrows dominantly volume transmission.

μ: Mu opioid receptor; 5-HT: Serotonin; 5-HT$_x$: Serotonin receptor; A_{2A}: Adenosine 2a receptor; ACh: Acetylcholine; DA: Dopamine; DRN: Dorsal raphe nucleus; D_x: DA receptor; ENK: Metenkephalin; FSI: Fast-spiking interneuron; $GABA_A$: $GABA_A$ receptor; Glu: Glutamate; GPe: Globus pallidus pars externa; H: Histamine; H_x: Histamine receptor; LC: Locus coeruleus; LTN: Laterodorsal tegmental nucleus; LTS: Low-treshold spiking interneuron; MSN: Medium-sized spiny neuron; M_x: Muscarinic acetylcholine receptor; NA: Noradrenaline; nACh: Nicotinic acetylcholine receptor; NO: Nitrogen monoxide; NPY: Neuropeptide Y; PPN: Pedunculopontine nucleus; SNpc: Substantia nigra pars compacta; SOM: Somatostatin; SP: Substance P; α_2: Alpha-2 adrenergic receptor; β_1: Beta-1 adrenergic receptor; δ: Delta opioid receptor; κ: Kappa opioid receptor.

DaT-SCAN™ (a single photon emission computed tomography using ^{123}I-ioflupane as dopamine transporter ligand; GE Healthcare) does not include its applicability in the differential diagnosis between iPD and DIP [33], some evidence suggest that it still might be a reliable technique for that purpose [34,35]. Similarly, other radiopharmacons can also be utilised [36]. The application of smell test for the evaluation of olfactory function or cardiac metaiodobenzylguanidine scintigraphy for the assessment of myocardial sympathetic innervation may also be helpful, as a significant impairment in the olfactory function and the uptake of the radiopharmaceutical are typical of iPD but not of DIP [37,38]. With regard to tardive Parkinsonism, although the Parkinsonian features persist for years after the discontinuation of the offending agent, the DaT-SCAN™ is normal [4].

The most common cause of DIP is related to antipsychotic medications [39]. Although second- or third-generation antipsychotics have a better side-effect profile than those from the first-generation group, they can also provoke DIP when applied in higher doses [40,41], except clozapine, in the case of which the risk of developing DIP is the same as in the case of placebo [42]. Surprisingly, not only the generation of the offending antipsychotics but the treated disease itself can influence the severity of DIP; for example, patients with affective disorders are more prone to develop DIP compared to patients with schizophrenia [43]. The pathomechanism of DIP due to antipsychotics is the blockade of striatal D_2 dopaminergic receptors in an extent higher than 75 – 80% [44]. Other dopamine receptor blocking agents (DRBAs), such as benzamide derivative anti-emetics (e.g., metoclopramide [45]), dopamine synthesis blockers (e.g., α-methyldopa [46]) or VMAT inhibitors (e.g., tetrabenazine [47]) can also induce DIP. Certain calcium channel antagonists (e.g., flunarizine or cinnarizine) can accompany the development of DIP as well, via decreasing neuronal activity and thereby reducing monoaminergic neurotransmission [48]. Furthermore, in rare occasions, anti-epileptics (e.g., valproate [49]) mood stabilisers (e.g., lithium [50]), anti-arrhythmics (e.g., amiodarone [51]), antidepressants (e.g., some selective serotonin reuptake inhibitors [SSRIs] [52,53]), immunosuppressants (e.g., cyclosporine [54]),

statins (e.g., lovastatin [55]), anticholinergics (e.g., propiverine [56]) and antimicrobials (e.g., amphotericin B [57]) have also been associated with DIP.

The treatment of DIP is challenging for the clinicians. First of all, the reduction of dose may offer some help; however, in most cases the substitution of the offending agent with a medication that has a better side-effect profile would be necessary [1]. Levodopa, dopamine agonists or anticholinergics usually have no effect [28]. In approximately 25% of patients with suspected DIP, a symptomatic relief cannot be achieved and a differentiation of these cases from 'pure' DIP is necessary [58]. These complicated cases presenting with persistent or progressive Parkinsonism may predominantly represent a preclinical stage of iPD or other degenerative conditions associated with Parkinsonism or a condition developed owing to the direct neurotoxic effect of the offending agent to the nigrostriatal dopaminergic neurons [59].

Parkinsonism-hyperpyrexia syndrome (PHS) is a rare condition mainly caused by a rapid reduction or withdrawal of anti-Parkinsonian medications [1]. The condition is characterised by severe akinesia, altered mental state and drowsiness, dysautonomia and fever with elevated level of creatine kinase, and may be precipitated by respiratory tract infection, acute gastrointestinal problems or traumatic injuries [60]. A slow symptomatic relief can be achieved in PHS after the restoration of previously applied treatment, in some severe cases; however, only subcutaneous apomorphine injections or intravenous amantadine infusions may offer some help, if any.

3.3 Drug-induced tremor

The onset of drug-induced tremor (DIT) is typically temporally related to the initiation of the therapy and the applied dose positively correlates with the extent of tremor [61]. However, the establishment of the diagnosis of DIT should be preceded by the careful exclusion of conditions with a progressive disease course (e.g., in cases of Parkinsonian, essential, tumour-related tremors) and the possible presence of other underlying medical conditions (e.g., hyperthyreoidism, hypoglycemia, vascular lesion, multiple sclerosis). Almost all types of tremor, that is, presenting at rest or action (postural, kinetic and intention) can be induced by medicines [62]. Furthermore, they can occur in a combination as well. Anti-arrhythmics (e.g., amiodarone – postural [63]), antimicrobial agents (e.g., trimethoprim-sulfamethoxazole – resting [64]), antidepressants (e.g., amitriptyline and SSRIs – postural and resting [65,66]), mood stabilisers (e.g., lithium – postural, intention and resting [67]), anti-epileptics (e.g., valproate – postural and resting [68]), bronchodilators (e.g., salbutamol – postural and intention [69]), chemotherapeutics (e.g., cytarabine, thalidomide – postural, intention and resting, respectively [70,71]), gastrointestinal drugs (e.g., metoclopramide – postural and resting [72,73]), hormones (e.g., levothyroxine overdose – postural [74]), immunosuppressants (e.g., cyclosporine – postural and intention [75]), psychostimulants (e.g., methylphenidate – postural [76]), antipsychotics and VMAT inhibitors (e.g., haloperidol and tetrabenazine – postural and resting [77,78]) can all evoke DIT, sometimes as part of DIP. Therapeutic approaches are similar to that described in DIP, that is, first a reduction of dose or switching to a medication with a lower ability to induce tremor is suggested. If necessary, evidence indicates that propranolol may improve drug-induced action tremor, whereas anticholinergics and amantadine might ameliorate drug-induced resting tremor [1,61]. With regard to tardive tremor, VMAT inhibitors (e.g., tetrabenazine) can be applied in the absence of Parkinsonian features [79].

3.4 Drug-induced chorea (± athetosis and ballismus)

Chorea, athetosis and ballismus are usually hardly distinguishable from each other; however, some distinctions can be made by the speed and the location of abnormal involuntary movements. Therefore, in this review, the discussion is limited to drug-induced chorea (DIC), keeping in mind that the below listed offending agents can evoke an overlapping spectrum of the chorea/athetosis/ballismus triad. The most common causes of DIC are levodopa and antipsychotics [17,80,81]. Levodopa results in the development of levodopa-induced dyskinesia (LID) in ~ 40% of patients with iPD after 4 – 6 years of use [82]. The most important risk factors for the development of LID are proposed to be the duration of disease and the dose of levodopa [83]. With regard to the pathomechanism of LID, maladaptive corticostriatal synaptoplasticity seems to be one of the most important factors [17,84]. Tardive chorea is rarely seen as the only side effect of neuroleptics, as it usually accompanies the classic oro-bucco-lingual TD. However, it can manifest after the discontinuation of DRBAs in children in the form of withdrawal emergent syndrome [16]. There are some differences between choreas induced by antipsychotics or levodopa [85]. In antipsychotics-induced cases, elderly people and females are more prone to develop chorea in contrast to levodopa-induced cases, where young patients are more sensitive and there is no difference between genders.

Several kinds of anti-epileptics (e.g., phenytoin [86]) have been reported to induce chorea on rare occasions. Tricyclic and SSRI antidepressants have both been linked to DIC [87] via the reduction of serotonergic attenuation of dopaminergic transmission [88]. With regard to oral contraceptives, both estrogen- and progesterone-containing pills can result in the development of choreiform movements [89]. The underlying proposed pathomechanism is that these medications result in an enhanced dopaminergic effect in the basal ganglia [90]. Psychostimulants (e.g., methylphenidate [91]) are capable of inducing chorea on the one hand by enhancing the presynaptic striatal dopamine release, and on the other hand by the inhibition of dopamine uptake by dopamine transporters [92]. DIC may also develop due to anticholinergics (e.g., trihexyphenidyl [93]), probably via the inhibition of central acetylcholine receptors. Antihistamines (e.g., cyproheptadine [94]) represent a probably uncommon cause of DIC with a currently unknown pathomechanism. Existing hypotheses

include a competitive inhibition of histamine receptors in the basal ganglia as a possible mechanism of action [95]. Rarely, other medications, such as opioids (e.g., methadone [96]), anti-arrhythmics (e.g., digoxin [97]), mood stabilisers (e.g., lithium [98]), antimetabolites (e.g., methotrexate [99]), anti-rheumatics (e.g., sulphasalazine [100]), anaesthetics (e.g., propofol [101]) and central muscle relaxants (e.g., baclofen [102]), are also capable of inducing DIC.

Acute or subacute DIC mostly disappears after the discontinuation of the offending agent [1]. Being a self-limiting condition, withdrawal emergent syndrome usually does not require any treatment either [4]. However, if necessary, the DRBAs can be reinstituted and tapered off gradually.

3.5 Drug-induced dystonia

ADRs are mostly observed following an exposure to DRBAs [1], that is, to antipsychotics (predominantly those belonging to the first generation [103,104]), to anti-emetics and to gastrointestinal promotility agents. However, the occurrence of ADR may also be linked to antidepressants (e.g., SSRIs, probably via the overstimulation of serotonin 5-HT_2 receptors in the basal ganglia [87,105]), and calcium channel blockers (e.g., nifedipine, probably via altering central dopamine production through N-type calcium channels [106,107]). On rare occasions, opioids (e.g., fentanyl [108]), psychostimulants (e.g., methylphenidate [109]), acetylcholinesterase (AChE) inhibitors (e.g., rivastigmine, via the proposed indirect inhibition of striatal D_1 dopaminergic receptors through the overstimulation of muscarinic M_4 receptors [110,111]), and surprisingly anticholinergics as well (e.g., benztropine [112]), antimicrobials (e.g., albendazole [113]), anti-epileptics (e.g., carbamazepine [114]), antihistamines (e.g., cetirizine [115]), benzodiazepines (e.g., midazolam [116]), histamine H_2 receptor blockers (e.g., ranitidine [117]), chemotherapeutic agents (e.g., 5-fluorouracil [118]), NSAIDs (e.g., ibuprofen [119]) and anaesthetics (e.g., propofol [120]) can also induce dystonic reactions. Although drug-induced dystonia (DID) predominantly affects craniocervical muscles resulting in torticollis, retrocollis or oromandibular dystonia [1,121], it can manifest in trismus, laryngospasm, pharyngeal dystonia, oculogyric crisis and limb dystonia as well [87]. In severe cases of ADR, the cessation of use of the offending agents is usually insufficient; however, they dramatically respond to intravenous or intramuscular injections of anticholinergic drugs [1]. If adequately repeated doses of anticholinergics are not effective, benzodiazepines (e.g., diazepam) may also be tried [107]. Furthermore, botulinum toxin injections may also serve as a therapeutic option in certain focal dystonias [122]. In the diferential diagnosis in tardive dystonia, there are some valuable features distinguishing them from idiopathic cases [123]. For example, DID is mainly restricted to the oromandibular region and is more frequently accompanied by stereotypies in the limbs and oro-facial-lingual region as well as akathisia and respiratory dyskinesias compared to idiopathic forms, where a coexistent cervical dystonia is more frequently present. In tardive dystonia, the administration of tetrabenazine or the application of a DRBA with minimal potency of worsening TD (e.g., clozapine) may be the first therapeutic choice [27]. In case the appropriate symptom control cannot be achieved by the selected anti-dopaminergic medications, anticholinergic medications can also be tried. If pharmaceutical treatment is ineffective, pallidal deep brain stimulation can be considered.

3.6 Drug-induced ataxia

Depending on the predominantly affected region of the nervous system, ataxia can be classified into three subtypes: cerebellar, vestibular and sensory. Drug-induced ataxia (DIA) can occur as a result of a temporary or permanent dysfunction of these systems alone [124] or in combination. DIA can be caused by benzodiazepines with hypnotic effect (e.g., flunitrazepam [125]), barbiturates (e.g., phenobarbital [126]), sleeping pills (e.g., zolpidem [127]), central muscle relaxants (e.g., baclofen [128]), anti-epileptics (e.g., carbamazepine [129], pregabalin [130] and gabapentin [131]) and anaesthetics (e.g., propofol [124]) via a significant reduction of neuronal firing in the cerebellum. However, some anti-epileptics (e.g., phenytoin [132]), mood stabilisers (e.g., lithium [124]) and immunosuppressants (e.g., cyclosporine [124]) can result in cerebellar damage and permanent ataxia. Furthermore, there are some groups of agents, such as antidepressants (e.g., clomipramine [124]), hormones (e.g., fluoxymesterone [124]) and antihyperlipidemics (e.g., atorvastatin [124]), which induces cerebellar ataxia with an unknown mechanism of action. Some of the agents that have ototoxic effects might have an accompanying vestibulotoxic effect as well, mimicking the development of a cerebellar syndrome [133]. Some antimicrobials (e.g., gentamycin [134]) and chemotherapeutics (e.g., vincristine [135]) have proved to exert such vestibulotoxic effects. Medication-induced sensory- or mixed neuropathies may both be responsible for a sensory ataxia [136]. From this aspect, the major offending agents are chemotherapeutics (e.g., cisplatin [136]), statins [137], anti-arrhythmics (e.g., amiodarone [138]) and antimicrobials (e.g., nucleoside analogues [139]). The harm is related to the neurotoxic effect of these drugs.

From a therapeutic point of view, considering the neurotoxic properties of the offending agents, the prevention of the development of DIA would be a major aim, that is, these drugs should be applied in as low dose and for as short duration as possible.

3.7 Drug-induced myoclonus

When talking about myoclonus, a distinction between positive and negative (i.e., asterixis) myoclonus should be made. The group of the most common offending agents related to drug-induced positive myoclonus (DIPM [140]) consists of antibiotics (e.g., quinolones), antidepressants (e.g., SSRIs), anxiolytics (e.g., benzodiazepines) and opioids (e.g., morphine). Furthermore, anti-Parkinsonian agents

(e.g., levodopa [141]), DRBAs (e.g., clozapine [142] and metoclopramide [143]), AChE inhibitors (e.g., donepezil [144]), anti-epileptics (e.g., carbamazepine [145]), calcium channel blockers (e.g., amlodipine [146]), anti-arrhythmics (e.g., amiodarone [147]), chemotherapeutics (e.g., 5-fluorouracil [148]), NSAIDs (e.g., diclofenac [149]) and anaesthetics (e.g., etomidate [150]) can evoke DIPM, as well. Tardive positive myoclonus typically occurs in the upper extremities [151]. DIPM usually ceases after the discontinuation of the offending agent.

In the case of a drug-induced asterixis, anti-epileptics represent the most common cause when their serum levels reach a toxic range [87]. Therefore, the proper therapeutic approach is dose reduction.

3.8 Drug-induced tic

Tic, which is a rapid stereotyped movement and/or vocalisation, can be provoked by several pharmaceutical agents [87]. These drugs include psychostimulants (e.g., methylphenidate [152]), antidepressants (e.g., SSRIs [153]), antipsychotics (e.g., thioridazine [154]) and anti-epileptics (e.g., carbamazepine [155]). Of note, the latter one does not resolve after the discontinuation of the offending agent, but improves with the application of haloperidol.

3.9 Other specific drug-induced conditions

Akathisia, which can be described as an intense inner urge to move, that is, the strong feeling of restlessness [1], can occur as an acute or chronic DIMD, and sometimes in the form of a tardive syndrome [4]. The offending agents are DRBAs [156], antidepressants [157] or psychostimulants (e.g., atomoxetine [158]). The development of akathisia is also influenced by the treated disease itself, as previously described in the case of DIP [43]. Acute akathisia can be stopped by dose reduction or the discontinuation of the drug that evoked it. However, when these actions cannot be implemented, anticholinergics, β-blockers, benzodiazepines, amantadine, mirtazapine or clonidine can yield some relief [1].

Although classic TD represent the most common form of tardive strereotypy, stereotypic movements can occur in the limbs as well, as a result of neuroleptic side effect [4].

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to DRBAs (on dose escalation or a sudden withdrawal of stable doses) with potentially severe consequences [1]. The typical symptoms of NMS include fever, autonomic instability, altered mental state and certain movement disorders (rigidity, tremor, dystonia and myoclonus). The characteristic laboratory findings include elevated serum creatine kinase, elevated liver enzymes, leukocytosis, electrolyte disturbance, altered renal functions and coagulation. These may be accompanied by electrocardiographic abnormalities. To improve the diagnostic workup, the Delphi consensus method has been established [159]. The therapeutic approaches comprise an immediate discontinuation of the offending agent, the introduction of dopaminergic agonists and supportive care if necessary. Dantrolene and benzodiazepines may also provide beneficial effects with regard to rigidity and rhabdomyolysis. The duration of treatment should be long enough to prevent a relapse.

Serotonin syndrome represents another acute drug-induced condition resembling NMS [1]. The offending agents are those that increase serotonergic activity, for example, SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, opioids and anti-epileptics [160]. The characteristic symptoms include agitation, anxiety, confusion or euphoria, dysautonomia with fever, tachycardia, elevated blood pressure, tachypnea, diaphoresis and diarrhoea and certain movement disorders (tremor, akathisia, myoclonus and rigidity). From therapeutic aspect, in case the immediate discontinuation of the culprit medication is not enough to achieve symptomatic relief, benzodiazepines (e.g., diazepam) or serotonin 5-HT_{2A} receptor antagonist (e.g., cyproheptadine) can be applied in severe cases.

Restless legs syndrome (RLS), periodic limb movements of sleep (PLMS) and rapid eye movement (REM) sleep behaviour disorder/REM sleep without atonia (RBD/RSWA) can all manifest as medication-induced movement disorders as well [161]. Antidepressants (e.g., SSRIs [162]), mood stabilisers (e.g., lithium [163]), levodopa/carbidopa [164], hormones (e.g., L-thyroxine [165]), antipsychotics (e.g., olanzapine [166] and quetiapine [167]), anti-epileptics (e.g., phenytoin [168]), and histamine H_2 receptor blockers (e.g., cimetidine [169]) can all evoke RLS, which can be characterised by a strong urge to move the lower limbs at rest or inactivity in the evening or at night that relieve with movement. Furthermore, opioids (e.g., tramadol), which would primarily serve as a treatment option for RLS, can cause the augmentation of the condition, as well [170]. With regard to drug-induced PLMS, which are repetitive movements typically in the lower limbs, several kinds of antidepressants (e.g., tricyclics [171]) can be identified as culprits. In addition to antidepressants (e.g., SSRIs [172]), monoaminooxidase B inhibitors (e.g., selegiline [173]) and β-adrenoreceptor antagonists (e.g., bisoprolol [174]) can serve as offending agents in the background of drug-induced RBD/RSWA, which is characterised by a complex pathological motor behaviour during REM sleep. The first-line intervention in cases of RLS, PLMS and RBD/RSWA should be the cessation of the offending agents [161].

Myokymia, which is an involuntary trembling of few muscles or some bundles within a muscle without changing the position of joints, can be evoked by calcium channel blockers (e.g., flunarizine [175]), antimicrobials (e.g., cefepime [176]), antirheumatics (e.g., gold [177]), chemotherapeutics (e.g., oxaliplatin [178]) and fibrates (e.g., clofibrate [179]) as well.

Drug-induced myorhythmia is an extremely rare condition; it has been reported only as a side effect of INFα2a therapy [180].

4. Conclusions

DIMDs represent a specific aspect of patient care. On the one hand, the significance of DIMDs is that they generally

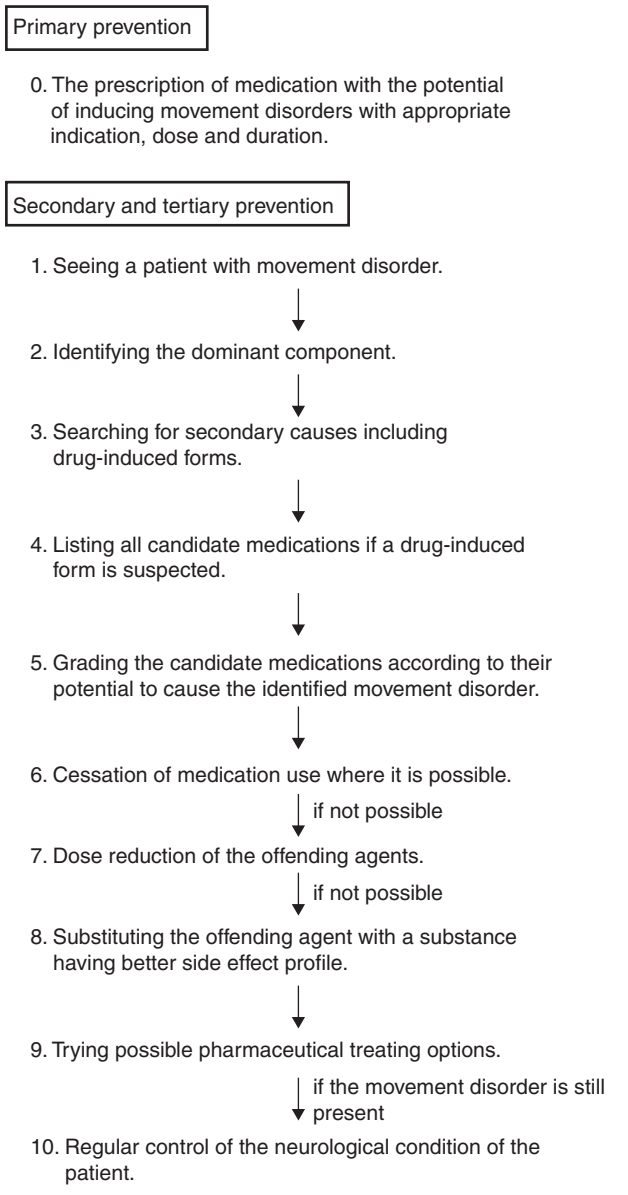

Figure 2. The proposed scheme for physicians to the prevention of drug-induced movement disorders.

represent a potentially treatable condition among a group of reminiscent disorders where merely symptomatic therapy is available if any. Therefore, when a patient with a relatively recent-onset movement disorders is observed, the possibility of DIMDs should always be considered among other secondary and treatable conditions. Furthermore, on the other hand, physicians should be very cautious with the application of medications with the potential of inducing serious side effects that include movement disorders. From this aspect, these kinds of medications are ought to be applied for as short duration and in as low dose as the appropriate management and the condition of the patients allows.

5. Expert opinion

In recent years, significant improvements have been achieved with regard to the side-effect profile of key groups of pharmaceutical agents (e.g., antipsychotics, antidepressants and gastrointestinal agents). Although the development of new generations of these kinds of drugs may help in the prevention or reduction of the frequency of DIMDs, most of them cannot provide complete safety. Furthermore, there are other groups of medications (e.g., antimicrobials, chemotherapeutics) where drug development mainly aims at the preservation or improvement of effectiveness without worsening the side-effect profile. Therefore physicians often face the challenge to achieve the required therapeutic effect with only minimal side effect. However, the appropriate dosing should be determined ubiquitously on individual basis, because the knowledge is still insufficient to determine why some patients are relatively resistant to therapeutic doses of drugs with the potential of evoking DIMDs, whereas others are not. One of the underlying factors could be the inadequate plasma drug concentrations due to inter-individual variability in metabolism. Accordingly, in addition to drug development, a special attention should be paid to the exploration of genetic and environmental factors influencing drug responsiveness, interactions and side-effect profile.

The next most important aspect of DIMDs is the fact that they are frequently overlooked by the clinical community. This issue holds special importance, because most of DIMDs are potentially reversible with the cessation of treatment, reduction of dose or substituting the offending agent with a substance having better side-effect profile. From this point of view, much more efforts should be made by movement disorder specialists and pharmacists for the dissemination of knowledge essential for the establishment of the right diagnosis and the management of DIMDs (**Figure 2**). Furthermore, the prescription of drugs with potentially serious side effects should be restricted to experts in the respective fields, because many drugs in relation to DIMDs are prescribed with inappropriate indication, dose and duration.

With regard to reducing the prevalence of DIMDs the following considerations should be kept in mind in relation to the subsequent groups of pharmaceutical agents where the choice of drug or dose have special implications: i) antipsychotics: the preferred use of second- and third-generation agents in low therapeutic doses instead of first-generation agents with higher risk of inducing movement disorders; ii) mood stabilisers: paying close attention to the narrow therapeutic range of lithium; iii) calcium channel blockers: the preferred use of new generation agents with better side-effect profile; iv) gastrointestinal agents: the preferred use of new generation agents (e.g., famotidine rather than cimetidine or ranitidine) with lower penetration through the blood-brain barrier (e.g., domperidon rather than metoclopramide); v) anti-epileptics: paying close attention to the

proper application of drugs keeping serum levels in therapeutic ranges; vi) antimicrobials: targeted antimicrobial therapy in the appropriate dose for only the necessary duration; vii) opioids: only when NSAIDs are not effective as pain killers; and viii) hypnotics: the preferred application of non-benzodiazepine hypnotics.

Most of DIMDs are related to the unspecific adverse action of the offending agents in the basal ganglia and in the cerebellum. Therefore future research should aim not only at the development of drugs with much higher selectivity and better side-effect profile, but also at the better characterisation of neurochemical profile of the affected functional systems.

Declaration of interest

This work was supported by the projects TÁMOP-4.2.2. A-11/1/KONV-2012-0052, MTA-SZTE Neuroscience Research Group and Hungarian Brain Research Program – Grant No. KTIA_NAP_13-A_III/9. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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