
Drug-induced movement disorders

Authors: Dénes Zádorí¹, Gábor Veres¹, Levente Szalárda¹, Péter Klivényi¹, László Vécsei¹,²

Affiliations:
¹Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Semmelweis u. 6, H-6725 Szeged, Hungary
zadori.denes@med.u-szeged.hu, veresg_gytk@gmail.com, szalardy.levente@med.u-szeged.hu, klivenyi.peter@med.u-szeged.hu, vecsei.laszlo@med.u-szeged.hu
²MTA-SZTE Neuroscience Research Group, Semmelweis u. 6, H-6725 Szeged, Hungary

Running title:
Drug-induced movement disorders

Corresponding author:
László Vécsei MD, PhD, DSc
Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged,
Semmelweis u. 6, H-6725 Szeged, Hungary
Phone:+36(62)545351; Fax: +36(62)545597
E-mail: vecsei.laszlo@med.u-szeged.hu
Abstract

Drug-induced movement disorders (DIMDs) can be elicited by several kinds of pharmaceutical agents. The major groups of offending drugs include antipsychotics, antidepressants, calcium channel blockers, antiepileptics, gastrointestinal drugs, mood stabilizers, antimicrobials, antiarrhythmics and chemotherapeutic agents among others. Although the number of offending agents and reported cases are variable, on the whole, all kinds of movement disorders can be evoked by pharmaceuticals. Therefore, when we observe a patient with a movement disorder of relatively recent onset, the possibility of DIMDs should always be considered among other secondary and treatable conditions. As the treatment of some DIMDs is quite challenging, a preventive approach is preferable. Accordingly, we should be very cautious with the prescription of pharmaceuticals that are able to induce severe adverse effects, i.e. their use should be strictly limited to appropriate indications and they should be applied in as low doses as the patient’s condition allows and only for the shortest adequate duration. 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 characterization of the neurochemical profile of the affected functional systems, in addition to the development of drugs with higher selectivity and better side-effect profile. Furthermore, special attention should be paid to the exploration of genetic and environmental factors influencing drug responsiveness, interactions and side-effect profile.

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

Most of DIMDs are related to an unspecific adverse action of the offending agents in the basal ganglia and the cerebellum; therefore, better characterization 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: i.e. 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.
**Abbreviations**

AChE – acetylcholinesterase  
ADR – acute dystonic reaction  
Ca\(^{2+}\) – calcium  
DA – dopamine  
DIA – drug-induced ataxia  
DIC – drug-induced chorea  
DID – drug-induced dystonia  
DIM – drug-induced myoclonus  
DIMD – drug-induced movement disorder  
DIP – drug-induced parkinsonism  
DIPM – drug-induced positive myoclonus  
DIT – drug-induced tremor  
DITic – drug-induced tic  
GABA – gamma-aminobutyric acid  
H\(_2\) – histamine-2 receptor  
INFα2a – interferon alpha-2a  
iPD – idiopathic Parkinson's disease  
LID – levodopa-induced dyskinesia  
NMS – neuroleptic malignant syndrome  
NSAID – non-steroid anti-inflammatory drug  
DRBA – dopamine receptor blocking agent  
PHS – parkinsonism-hyperpyrexia syndrome  
PLMS – periodic limb movements of sleep  
RBD – REM sleep behavior disorder
REM – rapid eye movement
RLS – restless legs syndrome
RSWA – REM sleep without atonia
SS – Serotonin syndrome
TD – tardive dyskinesias
VMAT – vesicular monoamine transporter
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]). The underlying pathomechanism is only known in a subset of DIMDs; however, an altered neurotransmission in the basal ganglia (predominantly in the striatum; Fig. 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. Drug-induced movement disorders

2.1 On the significance of tardive syndromes

Among chronic DIMDs, tardive dyskinesias (TDs) represent a rather specific subgroup [2,3]. TDs represent a group of neuroleptic-induced delayed-onset iatrogenic movement disorders, which can manifest in stereotypy, dystonia, akathisia, tic, tremor, myoclonus, chorea, parkinsonism, withdrawal emergent syndrome and neuroleptic malignant syndrome (NMS). 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 [2]. In addition to the exposure to neuroleptics (a duration- and dose-related effect [4]), older age [5], African-American ethnicity [6], the presence of diabetes mellitus [7] and the occurrence of acute
dystonic reactions or parkinsonism [4] may be the major predisposing risk factors for the development of TD. Even third-generation antipsychotics (e.g. aripiprazole [8]) have the potency to evoke TD. The proposed pathomechanisms of TD include dopamine 2 receptor upregulation with subsequent hypersensitivity, gamma-aminobutyric acid (GABA) insufficiency, increased endogenous opioid effect, glutamate excitotoxicity, oxidative stress and genetic susceptibility as well [2,3]. In addition to neuroleptics, antidepressants (e.g. duloxetine [9]), mood stabilizers (e.g. lithium [10]) and calcium channel blockers (e.g. flunarizine [11]) can also induce tardive syndromes. The prevalence of neuroleptic-induced TD is relatively high, reaching approximately 20% [12]. 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 neuroleptic drug [13]. 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, 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: we should be very cautious with the prescription of neuroleptics and they are 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 [14]. In general, with regard to the limited therapeutic options in TD, mostly vesicular monoamine transporter (VMAT) inhibitors (e.g. tetrabenazine [15]) amantadine [16], benzodiazepines (e.g. clonazepam [16]), anticholinergics (e.g. trihexyphenidyl [17]), beta-blockers (e.g. propranolol [18]), antiepileptics (e.g. levetiracetam [19]), chemodenervation with botulinum toxin injections [20] or deep brain stimulation [21,22] may come into account.
2.2 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 [23]. Therefore, the exclusion of idiopathic Parkinson’s disease (iPD [24]) in the differential diagnostic workup of DIP (the second most common cause of parkinsonism after iPD [25]) is essential. Fortunately, there are some valuable tools for this workup [26]. 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 favor the diagnosis of DIP [23,27]. Although the formal indication of DaT-SCAN™ (a single photon emission computed tomography using $^{123}$I-iodophane as dopamine transporter ligand; GE Healthcare) does not include its applicability in the differential diagnosis between iPD and DIP [28], some evidence suggest that it still might be a reliable technique for that purpose [29,30]. Similarly, other radiopharmaceuticals can also be utilized [31]. 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 olfactory function and the uptake of the radiopharmaceutical are typical of iPD but not of DIP [32,33]. With regard to tardive parkinsonism, although the parkinsonian features persist for years after the discontinuation of the offending agent, the DaT-SCAN™ is normal [2].

The most common cause of DIP is related to antipsychotic medications [34]. Although atypical antipsychotics have better side-effect profile than typical ones, they can also provoke DIP when applied in higher doses [35], except clozapine, in case of which the risk of developing DIP is the same as in case of placebo [36]. The pathomechanism of DIP due to antipsychotics is the blockade of striatal $D_2$ dopaminergic receptors in an extent higher than 75-80% [37]. Other dopamine receptor blocking agents (DRBAs), such as benzamide
derivative antiemetics (e.g. metoclopramide [38]), dopamine synthesis blockers (e.g. alphamethyldopa [39]) or VMAT inhibitors (e.g. tetrabenazine [40]) 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 [41]. Furthermore, in rare occasions, antiepileptics (e.g. valproate [42]) mood stabilizers (e.g. lithium [43]), antiarrhythmics (e.g. amiodarone [44]), antidepressants (e.g. some selective serotonin reuptake inhibitors (SSRIs) [45,46]), immunosuppressants (e.g. cyclosporine [47]), statins (e.g. lovastatin [48]) and antimicrobials (e.g. amphotericin B [49]) 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 better side-effect profile would be necessary [1]. Levodopa, dopamine agonists or anticholinergics usually have no effect [23]. 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 [50]. 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 [51]. Parkinsonism-hyperpyrexia syndrome (PHS) is a rare condition mainly caused by a rapid reduction or withdrawal of antiparkinsonian medications [1]. The condition is characterized 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 [52]. 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.

2.3 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 [53]. 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, tumor-related tremors) and the possible presence of other underlying medical conditions (e.g. hyperthyreoidism, hypoglycemia, vascular lesion, multiple sclerosis). Almost all types of tremor, i.e. presenting at rest or action (postural, kinetic and intention) can be induced by medicines [54]. Furthermore, they can occur in a combination as well. Antiarrhythmics (e.g. amiodarone – postural [55]), antimicrobial agents (e.g. trimethoprim-sulfamethoxazole – resting [56]), antidepressants (e.g. amitriptyline and SSRIs – postural and resting [57,58]), mood stabilizers (e.g. lithium – postural, intention and resting [59]), antiepileptics (e.g. valproate – postural and resting [60]), bronchodilators (e.g. salbutamol – postural and intention [61]), chemotherapeutics (e.g. cytarabine, thalidomide – postural, intention and resting, respectively [62,63]), gastrointestinal drugs (e.g. metoclopramide – postural and resting [64,65]), hormones (e.g. levothyroxine overdose – postural [66]), immunosuppressants (e.g. cyclosporine – postural and intention [67]), psychostimulants (e.g. methylphenidate – postural [68]) neuroleptics and VMAT inhibitors (e.g. haloperidol and tetrabenazine – postural and resting [69,70]) can all evoke DIT, sometimes as part of DIP. Therapeutic approaches are similar to that described in DIP, i.e. 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 [1,53]. With regard to tardive tremor, VMAT inhibitors (e.g. tetrabenazine) can be applied in the absence of parkinsonian features [71].

2.4 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 [14,72,73]. Levodopa results in the development of levodopa-induced dyskinesia (LID) in about 40% of patients with iPĐ after 4-6 years of use [74]. The most important risk factors for the development of LID are proposed to be the duration of disease and the dose of levodopa [75]. With regard to the pathomechanism of LID, maladaptive corticostriatal synaptoplasticity seems to be one of the most important factors [14,76]. 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 [13].

Several kinds of antiepileptics (e.g. phenytoin [77]) have been reported to induce chorea on rare occasions. Tricyclic and SSRI antidepressants have both been linked to DIC [78] via the reduction of serotonergic attenuation of dopaminergic transmission [79]. With regard to oral contraceptives, both estrogen- and progesterone-containing pills can result in the development of choreiform movements [80]. The underlying proposed pathomechanism is that these medications result in an enhanced dopaminergic effect in the basal ganglia [81]. Psychostimulants (e.g methylphenidate [82]) 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 [83]. DIC may also develop due to anticholinergics (e.g. trihexyphenidyl [84]), probably via the inhibition of central acetylcholine receptors. Antihistamines (e.g. cyproheptadine [85]) 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 [86]. Rarely, other medications, such as opioids (e.g. methadone [87]), antiarrhythmics (e.g. digoxin [88]), mood stabilizers (e.g. lithium [89]), antimetabolites (e.g. methotrexate [90]) and central muscle relaxants (e.g. baclofen [91]) 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 [2]. However, if necessary, the DRBAs can be reinstituted and tapered off gradually.

2.5 Drug-induced dystonia

Acute dystonic reactions (ADRs) are mostly observed following an exposure to DRBAs [1], i.e. to neuroleptics (predominantly the conventional ones [92,93]), to antiemetics and to gastrointestinal promotility agents. However, the occurrence of ADR may also be linked to antidepressants (e.g. SSRIs, probably via the overstimulation of serotonine 5-HT \textsubscript{2} receptors in the basal ganglia [78,94]), calcium channel blockers (e.g. nifedipine, probably via altering central dopamine production through N-type calcium channels [95,96]). On rare occasions, opioids (e.g. fentanyl [97]), psychostimulants (e.g. methylphenidate [98]), acetylcholinesterase inhibitors (e.g. rivastigmine, via the proposed indirect inhibition of striatal D\textsubscript{1} dopaminergic receptors through the overstimulation of muscarinic M\textsubscript{4} receptors [99,100]), antimicrobials (e.g. albendazole [101]), antiepileptics (e.g. carbamazepine [102]), antihistamines (e.g.
cetirizine [103]), benzodiazepines (e.g. midazolam [104]), histamine H₂ receptor blockers (e.g. ranitidine [105]), chemotherapeutic agents (e.g. 5-fluorouracil [106]), non-steroid anti-inflammatory drugs (NSAID, e.g. ibuprofen [107]) and anesthetics (e.g. propofol [108]) can also induce dystonic reactions. Although drug-induced dystonia (DID) predominantly affects craniocervical muscles resulting in torticollis, retrocollis or oromandibular dystonia [1,109], it can manifest in trismus, laryngospasm, pharyngeal dystonia, oculogyric crisis and limb dystonia as well [78]. 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 [96]. Furthermore, botulinum toxin injections may also serve as a therapeutic option in certain focal dystonias [110]. 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 [111]. In case the appropriate symptom control cannot be achieved by the selected antiparkinsonian medications, anticholinergic medications can also be tried. If pharmaceutical treatment is ineffective, pallidal deep brain stimulation can be considered.

2.6 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 or in combination. DIA can be caused by benzodiazepines with hypnotic effect (e.g. flunitrazepam [112]), barbiturates (e.g. phenobarbital [113]), sleeping pills (e.g. zolpidem [114]), central muscle relaxants (e.g. baclofen [115]) and antiepileptics (e.g. carbamazepine [116]) via a significant reduction of neuronal firing in the cerebellum. However, some antiepileptics (e.g.
phenytoin [117]) can result in cerebellar damage and permanent ataxia. Some of the agents that have ototoxic effects might have an accompanying vestibulotoxic effect as well, mimicking the development of a cerebellar syndrome [118]. Some antimicrobials (e.g. gentamycin [119]) and chemotherapeutics (e.g. vincristine [120]) have proved to exert such vestibulotoxic effects. Medication-induced sensory- or mixed neuropathies may both be responsible for a sensory ataxia [121]. From this aspect, the major offending agents are chemotherapeutics (e.g. cisplatin [121]), statins [122], antiarrhythmics (e.g. amiodarone [123]) and antimicrobials (e.g. nucleoside analogs [124]). 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, i.e. we should use these drugs in as low dose and for as short duration as possible.

2.7 Drug-induced myoclonus

When talking about myoclonus, we should distinguish between positive and negative (i.e. asterixis) ones. The group of the most common offending agents related to drug-induced positive myoclonus (DIPM [125]) consists of antibiotics (e.g. quinolones), antidepressants (e.g. SSRIs), anxiolytics (e.g. benzodiazepines) and opioids (e.g. morphine). Furthermore, antiparkinsonian agents (e.g. levodopa [126]), DRBAs (e.g. metoclopramide [127]), acetylcholinesterase inhibitors (e.g. donepezil [128]), antiepileptics (e.g. carbamazepine [129]), calcium channel blockers (e.g. amlodipine [130]), antiarrhythmics (e.g. amiodarone [131]), chemotherapeutics (e.g. 5-fluorouracil [132]) and anesthetics (e.g. etomidate [133]) can evoke DIPM, as well. Tardive positive myoclonus typically occurs in the upper extremities [134]. DIPM usually ceases after the discontinuation of the offending agent.
In case of a drug-induced asterixis, antiepileptics represent the most common cause when their serum levels reach a toxic range [78]. Therefore, the proper therapeutic approach is dose reduction.

2.8 Drug-induced tic

Tic, which is a rapid stereotyped movement and/or vocalization, can be provoked by several pharmaceutical agents [78]. These drugs include psychostimulants (e.g. methylphenidate [135]), antidepressants (e.g. amisulpride [136]) and antiepileptics (e.g. carbamazepine [137]). Of note, the latter one does not resolve after the discontinuation of the offending agent, but improves with the application of haloperidol.

2.9 Other specific drug-induced conditions

Akathisia, which can be described as an intense inner urge to move, i.e. the strong feeling of restlessness [1], can occur as an acute or chronic DIMD, and sometimes in the form of a tardive syndrome [2]. The offending agents are DRBAs. 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, beta-blockers, benzodiazepines, amantadine, mirtazapine or clonidine can yield some relief [1].

Although classic TD represent the most common form of tardive stereotypy, stereotypic movements can occur in the limbs as well, as a result of neuroleptic side-effect [2]. Neuroleptic malignant syndrome 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 ECG abnormalities. To improve the diagnostic workup, the Delphi consensus method has been established [138]. 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 (SS) represent another acute drug-induced condition resembling NMS [1]. The offending agents are those that increase serotonergic activity, e.g. SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, opioids and antiepileptics [139]. The characteristic symptoms include agitation, anxiety, confusion or euphoria, dysautonomia with fever, tachycardia, elevated blood pressure, tachypnea, diaphoresis and diarrhea 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 behavior disorder/REM sleep without atonia (RBD/RSWA) can all manifest as medication-induced movement disorders as well [140]. Antidepressants (e.g. SSRIs [141]), mood stabilizers (e.g. lithium [142]), levodopa/carbidopa [143], hormones (e.g. L-thyroxine [144]), antipsychotics (e.g. olanzapine [145]), antiepileptics (e.g. phenytoin [146]), histamine H$_2$ receptor blockers (e.g. cimetidine [147]) and opioids (e.g. tramadol [148]) can all evoke RLS, which can be characterized by a strong urge to move the lower limbs at rest or an inactivity in the evening or at night that relieve with movement. With regard to drug-induced
PLMS, which are repetitive movements typically in the lower limbs, several kinds of antidepressants (e.g. tricyclics [149]) can be identified as culprits. In addition to antidepressants (e.g. SSRIs [150]), monoaminooxidase B inhibitors (e.g. selegiline [151]) and beta-adrenoreceptor antagonists (e.g. bisoprolol [152]) can serve as offending agents in the background of drug-induced RBD/RSWA, which is characterized by a complex pathological motor behavior during REM sleep. The first line intervention in cases of RLS, PLMS and RBD/RSWA should be the cessation of the offending agents [140].

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 [153]), antimicrobials (e.g. cefepime [154]), antirheumatics (e.g. gold [155]) and fibrates (e.g. clofibrate [156]) as well. Drug-induced myorhythmia (i.e. Holmes tremor) is an extremely rare condition, it has been reported only as a side-effect of interferon alpha-2a therapy [157].

3. Conclusions

DIMDs represent a specific aspect of patient care. On the one hand, the significance of DIMDs is that they generally represent a potentially treatable condition among a group of reminiscent disorders where merely symptomatic therapy is available if any. Therefore, when we observe a patient with a relatively recent-onset movement disorders, the possibility of DIMDs should always be considered among other secondary and treatable conditions. Furthermore, on the other hand, we 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.
4. 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 we 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 we still lack the knowledge to determine why some patients are relatively resistant to therapeutic doses of drugs with the potential of evoking DIMDs while others are not.

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. 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: 1) neuroleptics: the preferred use of atypical agents in low therapeutic doses; 2) mood stabilizers: paying close attention to the narrow therapeutic range of lithium; 3) calcium channel blockers: the preferred use of new generation agents with better side-effect profile; 4) 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); 5) antiepileptics: paying close attention to the proper application of drugs keeping serum levels in therapeutic ranges; 6) antimicrobials: targeted antimicrobial therapy in the appropriate dose for only the necessary duration; 7) opioids: only when NSAIDs are not effective as pain killers; 8) 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 characterization 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 conflict of interest that is directly relevant to the content of this review.

**Bibliography**
Papers of special note have been highlighted as either of interest (•) or of considerable interest (★★) to readers


★★ Interesting review on some drug-induced movement disorders with acute or subacute onset.


★★ A well-detailed review on tardive syndromes.


★★ An excellent review on the clinical features and treatment algorithms of tardive syndromes.


• An interesting review about levodopa-induced and antipsychotic-induced dyskinesias.


**An interesting review on drug-induced parkinsonism with expert opinion.**


**A review about the value of certain tests in the differentiation of drug-induced parkinsonism and idiopathic Parkinson's disease.**


30. Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2013;84:1288-95
40. Giladi N, Melamed E. Levodopa therapy can ameliorate tetrabenazine-induced parkinsonism. Mov Disord 1999;14:158-9
42. Masmoudi K, Gras-Champel V, Masson H, Andrejak M. Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. Pharmacopsychiatry 2006;39:9-12

• A well-detailed review on tremorogenic drugs.


74. Ahl-skog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-58


**A detailed review on case reports of drug-induced chorea, dystonia, tic, tremor and myoclonus.**


84. Horn S, Hinson M, Morrissey M, Goetz CG. Blinded evaluation for the frequency of chorea in dystonia patients both on and off anticholinergic medication. Mov Disord 2002;17:S276-7

85. Samie MR, Ashton AK. Choroathetosis induced by cyproheptadine. Mov Disord 1989;4:81-4


98. Gay CT, Ryan SG. Paroxysmal kinesigenic dystonia after methylphenidate administration. J Child Neurol 1994;9:45-6


103. Esen I, Demirpence S, Yis U, Kurul S. Cetirizine-induced dystonic reaction in a 6-year-old boy. Pediatr Emerg Care 2008;24:627-8

104. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. BMJ 1990;300:614


119. Ding D, Jiang H, Salvi RJ. Mechanisms of rapid sensory hair-cell death following co-administration of gentamicin and ethacrynic acid. Hear Res 2010;259:16-23


123. Fraser AG, McQueen IN, Watt AH, Stephens MR. Peripheral neuropathy during long-term high-dose amiodarone therapy. J Neurol Neurosurg Psychiatry 1985;48:576-8

• An epidemiologic assessment of drug-induced myoclonus.

127. Lu CS, Chu NS. Acute dystonic reaction with asterixis and myoclonus following metoclopramide therapy. J Neurol Neurosurg Psychiatry 1988;51:1002-3


• An interesting review on sleep-related drug-induced movement disorders.


150. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27:317-21


**Figure caption**

Figure 1. The schematic depiction of the neurochemical aspects of striatal architecture. (5-HT – serotonin, 5-HT$_x$ – serotonin receptor, $\alpha_2$ – alpha-2 adrenergic receptor, ACh – acetylcholine, AMPA – alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, A$_{2A}$ – adenosine 2a receptor, $\beta_1$ – beta-1 adrenergic receptor, $\delta$ – delta opioid receptor, DA – dopamine, DRN – dorsal raphe nucleus, $D_x$ – DA receptor, ENK – metenkephalin, FSI – fast-spiking interneuron, GABA – gamma-aminobutyric acid, GABA$_A$ – GABA$_A$ receptor, Glu – glutamate, GPe – globus pallidus pars externa, H – histamine, $H_x$ – histamine receptor, $\kappa$ – kappa opioid receptor, LC – locus coeruleus, LTN – laterodorsal tegmental nucleus, LTS – low-threshold spiking interneuron, $\mu$ – mu opioid receptor, $M_x$ – muscarinic acetylcholine receptor, MSN – medium-sized spiny neuron, NA – noradrenaline, nACh – nicotinic acetylcholine receptor, NMDA: N-methyl-D-aspartate receptor, NO – nitrogen monoxide, NPY – neuropeptide Y, PPN – pedunculopontine nucleus, SNpc – substantia nigra pars compacta, SOM – somatostatin, SP – substance P; glutamate, the black plain figures represent inhibition, while white plain figures excitation; the reduced size of plain figures or dashed arrows represent subdominant effect; the arrows represent synaptic connections, while boutons without arrows dominantly volume transmission)
Figure 1
Table 1. The list of pharmacological classes of drugs with the potency of inducing movement disorders.

<table>
<thead>
<tr>
<th>Group</th>
<th>DID</th>
<th>DIT</th>
<th>DIM</th>
<th>DIA</th>
<th>SS</th>
<th>Myokymia</th>
<th>RBD</th>
<th>RSWA</th>
<th>DITic</th>
<th>Akathisia</th>
<th>NM S</th>
<th>PLMS</th>
<th>Holmes tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antiemetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Chemotherapeutics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Ca(^{2+})-channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antiparkinson</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Psychostimulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>VMAT inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Antihyperlipidemetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Central muscle relaxants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>AChE inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>H(_2) receptor blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Group</td>
<td>DID</td>
<td>DIT</td>
<td>DIM</td>
<td>DIA</td>
<td>SS</td>
<td>Myokymia</td>
<td>RBD</td>
<td>RSWA</td>
<td>DITic</td>
<td>Akathisia</td>
<td>NM</td>
<td>PLMS</td>
<td>Holmes tremor</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
<td>----------</td>
<td>-----</td>
<td>------</td>
<td>-------</td>
<td>------------</td>
<td>----</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaesthetics</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping pills</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antirheumatics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFα2a inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchodilatators</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA synthesis blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>