EXPERT OPINION ON DRUG SAFETY 14:(6) pp. 877-890. (2015)

Drug-induced movement disorders

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Running title:

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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 –

Serotonine 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-ioflupane 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 radiopharmacons 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. alpha-methyldopa [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/ballismsus 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 iPD 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_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_1 dopaminergic receptors through the overstimulation of muscarinic M_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 H_2 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 anti-dopaminergic 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 strereotypy, 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

1. Burkhard PR. Acute and subacute drug-induced movement disorders. Parkinsonism Relat Disord 2014;20:S108-12

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

2. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N Y) 2013;3:e1-11

•• A well-detailed review on tardive syndromes.

3. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. Neurotherapeutics 2014;11:166-76

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

4. Woerner MG, Alvir JM, Saltz BL, et al. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998;155:1521-8

5. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995;52:756-65

6. Wonodi I, Adami HM, Cassady SL, et al. Ethnicity and the course of tardive dyskinesia in outpatients presenting to the motor disorders clinic at the Maryland Psychiatric Research Center. J Clin Psychopharmacol 2004;24:592-8

7. Woerner MG, Saltz BL, Kane JM, et al. Diabetes and development of tardive dyskinesia. Am J Psychiatry 1993;150:966-8

8. Goyal R, Devi SH. A case of aripiprazole induced tardive dyskinesia in a neuroleptic-naive patient with two years of follow up. Clin Psychopharmacol Neurosci 2014;12:69-71

9. Albayrak Y, Ekinci O. Duloxetine-associated tardive dyskinesia resolved with fluvoxamine: a case report. J Clin Psychopharmacol 2012;32:723-4

10. Chakrabarti S, Chand PK. Lithium - induced tardive dystonia. Neurol India 2002;50:473-5

11. Fabiani G, Pastro PC, Froehner C. Parkinsonism and other movement disorders in outpatients in chronic use of cinnarizine and flunarizine. Arq Neuropsiquiatr 2004;62:784-8

12. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 1982;39:473-81

13. Mejia NI, Jankovic J. Tardive dyskinesia and withdrawal emergent syndrome in children. Expert Rev Neurother 2010;10:893-901

14. Damier P. Drug-induced dyskinesias. Curr Opin Neurol 2009;22:394-9

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

15. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. Expert Rev Neurother 2006;6:7-17

16. Aia PG, Revuelta GJ, Cloud LJ, Factor SA. Tardive dyskinesia. Curr Treat Options Neurol 2011;13:231-41

17. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. Neurologist 2003;9:16-27

18. Factor SA. Propranolol therapy for tardive dyskinesia revisited. Mov Disord 2012;27:1703

19. Woods SW, Saksa JR, Baker CB, et al. Effects of levetiracetam on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2008;69:546-54

20. Hennings JM, Krause E, Botzel K, Wetter TC. Successful treatment of tardive lingual dystonia with botulinum toxin: case report and review of the literature. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1167-71

21. Damier P, Thobois S, Witjas T, et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. Arch Gen Psychiatry 2007;64:170-6

22. Zhang JG, Zhang K, Wang ZC. Deep brain stimulation in the treatment of tardive dystonia. Chin Med J (Engl) 2006;119:789-92

23. Lopez-Sendon J, Mena MA, de Yebenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf 2013;12:487-96

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

24. Vecsei L. Recent advances in Parkinson's disease. Ideggyogy Sz 2002;55:406-7

25. Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord 2006;21:800-8

26. Brigo F, Erro R, Marangi A, et al. Differentiating drug-induced parkinsonism from Parkinson's disease: an update on non-motor symptoms and investigations. Parkinsonism Relat Disord 2014;20:808-14

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

27. Lopez-Sendon JL, Mena MA, de Yebenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;29:105-18

28. Kagi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010;81:5-12

29. Vlaar AM, de Nijs T, Kessels AG, et al. Diagnostic value of 123I-ioflupane and 123I-iodobenzamide SPECT scans in 248 patients with parkinsonian syndromes. Eur Neurol 2008;59:258-66

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

31. Kanyo B, Argyelan M, Dibo G, et al. [Imaging of dopamine transporter with Tc99m-Trodat-SPECT in movement disorders]. Ideggyogy Sz 2003;56:231-40

32. Lee PH, Kim JS, Shin DH, et al. Cardiac 123I-MIBG scintigraphy in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry 2006;77:372-4

33. Lee PH, Yeo SH, Yong SW, Kim YJ. Odour identification test and its relation to cardiac 123I-metaiodobenzylguanidine in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry 2007;78:1250-2

34. Noyes K, Liu H, Holloway RG. What is the risk of developing parkinsonism following neuroleptic use? Neurology 2006;66:941-3

35. Rochon PA, Stukel TA, Sykora K, et al. Atypical antipsychotics and parkinsonism. Arch Intern Med 2005;165:1882-8

36. Friedman JH. Atypical antipsychotics in the EPS-vulnerable patient. Psychoneuroendocrinology 2003;28 Suppl 1:39-51

37. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry 1992;49:538-44

38. Benazzi F. Side-effects of benzamide derivatives. Int J Geriatr Psychiatry 1997;12:132

39. Strang RR. Parkinsonism occurring during methyldopa therapy. Can Med Assoc J 1966;95:928-9

40. Giladi N, Melamed E. Levodopa therapy can ameliorate tetrabenazine-induced parkinsonism. Mov Disord 1999;14:158-9

41. Terland O, Flatmark T. Drug-induced parkinsonism: cinnarizine and flunarizine are potent uncouplers of the vacuolar H+-ATPase in catecholamine storage vesicles. Neuropharmacology 1999;38:879-82

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

43. Dallocchio C, Mazzarello P. A case of Parkinsonism due to lithium intoxication: treatment with Pramipexole. J Clin Neurosci 2002;9:310-1

44. Dotti MT, Federico A. Amiodarone-induced parkinsonism: a case report and pathogenetic discussion. Mov Disord 1995;10:233-4

45. Stadtland C, Erfurth A, Arolt V. De novo onset of Parkinson's disease after antidepressant treatment with citalopram. Pharmacopsychiatry 2000;33:194-5

46. Pina Latorre MA, Modrego PJ, Rodilla F, et al. Parkinsonism and Parkinson's disease associated with long-term administration of sertraline. J Clin Pharm Ther 2001;26:111-2

47. Lima MA, Maradei S, Maranhao Filho P. Cyclosporine-induced parkinsonism. J Neurol 2009;256:674-5

48. Muller T, Kuhn W, Pohlau D, Przuntek H. Parkinsonism unmasked by lovastatin. Ann Neurol 1995;37:685-6

49. Fisher JF, Dewald J. Parkinsonism associated with intraventricular amphotericin B. J Antimicrob Chemother 1983;12:97-9

50. Marti Masso JF, Poza JJ. [Drug-induced or aggravated parkinsonism: clinical signs and the changing pattern of implicated drugs]. Neurologia 1996;11:10-5

51. Rollema H, Skolnik M, D'Engelbronner J, et al. MPP(+)-like neurotoxicity of a pyridinium metabolite derived from haloperidol: in vivo microdialysis and in vitro mitochondrial studies. J Pharmacol Exp Ther 1994;268:380-7

52. Onofrj M, Thomas A. Acute akinesia in Parkinson disease. Neurology 2005;64:1162-9

53. Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol 2005;4:866-76

• A well-detailed review on tremorogenic drugs.

54. Sirisena D, Williams DR. My hands shake--classification and treatment of tremor. Aust Fam Physician 2009;38:678-83

55. Charness ME, Morady F, Scheinman MM. Frequent neurologic toxicity associated with amiodarone therapy. Neurology 1984;34:669-71

56. Patterson RG, Couchenour RL. Trimethoprim-sulfamethoxazole-induced tremor in an immunocompetent patients. Pharmacotherapy 1999;19:1456-8

57. Raethjen J, Lemke MR, Lindemann M, et al. Amitriptyline enhances the central component of physiological tremor. J Neurol Neurosurg Psychiatry 2001;70:78-82

58. Wernicke JF. The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985;46:59-67

59. Gelenberg AJ, Jefferson JW. Lithium tremor. J Clin Psychiatry 1995;56:283-7

60. Karas BJ, Wilder BJ, Hammond EJ, Bauman AW. Valproate tremors. Neurology 1982;32:428-32

61. Nizet TA, Broeders ME, Folgering HT. Tremor side effects of salbutamol, quantified by a laser pointer technique. Respir Med 2004;98:844-50

62. Dworkin LA, Goldman RD, Zivin LS, Fuchs PC. Cerebellar toxicity following high-dose cytosine arabinoside. J Clin Oncol 1985;3:613-6

63. Chiruka S, Chapman CS. Severe tremors associated with use of thalidomide. Am J Hematol 2005;78:81-2

64. Kataria M, Traub M, Marsden CD. Extrapyramidal side-effects of metoclopramide. Lancet 1978;2:1254-5

65. Ahronheim JC. Metoclopramide and tremor. Ann Intern Med 1982;97:621

66. Beier C, Liebezeit B, Volkl TM, et al. [Attempted suicide with L-thyroxine in an adolescent girl]. Klin Padiatr 2006;218:34-7

67. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol 1999;246:339-46

68. Pataki CS, Carlson GA, Kelly KL, et al. Side effects of methylphenidate and desipramine alone and in combination in children. J Am Acad Child Adolesc Psychiatry 1993;32:1065-72

69. Yen YC, Lung FW, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:285-90

70. Lingjaerde O. Tetrabenazine (Nitoman) in the Treatment of Psychoses. With a Discussion on the Central Mode of Action of Tetrabenazine and Reserpine. Acta Psychiatr Scand 1963;39:SUPPL170:1-109

71. Stacy M, Jankovic J. Tardive tremor. Mov Disord 1992;7:53-7

72. Klivenyi P, Vecsei L. [Updates in practical neurology--I. The principles of modern levodopa therapy in Parkinson's disease]. Ideggyogy Sz 2007;60:61-4

73. Gardian G, Vecsei L. Medical treatment of Parkinson's disease: today and the future. Int J Clin Pharmacol Ther 2010;48:633-42

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

75. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 2000;123 (Pt 11):2297-305

76. Zadori D, Szalardy L, Toldi J, et al. Some molecular mechanisms of dopaminergic and glutamatergic dysfunctioning in Parkinson's disease. J Neural Transm 2013;120:673-81

77. Shulman LM, Singer C, Weiner WJ. Phenytoin-induced focal chorea. Mov Disord 1996;11:111-4

78. Zesiewicz TA, Sullivan KL. Drug-induced hyperkinetic movement disorders by nonneuroleptic agents. Handb Clin Neurol 2011;100:347-63

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

79. Chari S, Quraishi SH, Jainer AK. Fluoxetine-induced exacerbation of chorea in Huntington's disease? A case report. Pharmacopsychiatry 2003;36:41-3

80. Pulsinelli WA, Hamill RW. Chorea complicating oral contraceptive therapy. Case report and review of the literature. Am J Med 1978;65:557-9

81. Robottom BJ, Weiner WJ. Chorea gravidarum. Handb Clin Neurol 2011;100:231-5

82. Weiner WJ, Nausieda PA, Klawans HL. Methylphenidate-induced chorea: case report and pharmacologic implications. Neurology 1978;28:1041-4

83. Morgan JC, Winter WC, Wooten GF. Amphetamine-induced chorea in attention deficit-hyperactivity disorder. Mov Disord 2004;19:840-2

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. Choreoathetosis induced by cyproheptadine. Mov Disord 1989;4:81-4

86. Ellender TJ, Huerta-Ocampo I, Deisseroth K, et al. Differential modulation of excitatory and inhibitory striatal synaptic transmission by histamine. J Neurosci 2011;31:15340-51

87. Lussier D, Cruciani RA. Choreiform movements after a single dose of methadone. J Pain Symptom Manage 2003;26:688-91

88. Wedzicha JA, Gibb WR, Lees AJ. Chorea in digoxin toxicity. J Neurol Neurosurg Psychiatry 1984;47:419

89. Stemper B, Thurauf N, Neundorfer B, Heckmann JG. Choreoathetosis related to lithium intoxication. Eur J Neurol 2003;10:743-4

90. Necioglu Orken D, Yldrmak Y, Kenangil G, et al. Intrathecal methotrexate-induced acute chorea. J Pediatr Hematol Oncol 2009;31:57-8

91. van der Plas AA, van Rijn MA, van Hilten JJ. Baclofen-induced chorea in complex regional pain syndrome-related dystonia. Mov Disord 2010;25:959-60

92. Rybakowski JK, Vansteelandt K, Remlinger-Molenda A, et al. Extrapyramidal symptoms during treatment of first schizophrenia episode: results from EUFEST. Eur Neuropsychopharmacol 2014;24:1500-5

93. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics : incidence, prevention and management. Drug Saf 2005;28:191-208

94. Arnone D, Hansen L, Kerr JS. Acute dystonic reaction in an elderly patient with mood disorder after titration of paroxetine: possible mechanisms and implications for clinical care. J Psychopharmacol 2002;16:395-7

95. de Medina A, Biasini O, Rivera A, Sampera A. Nifedipine and myoclonic dystonia. Ann Intern Med 1986;104:125

96. Pina MA, Ara JR, Remirez A, Castiella J. Verapamil and acute dystonia. J Clin Pharm Ther 1998;23:79-80

97. Zesiewicz TA, Hauser RA, Freeman A, et al. Fentanyl-induced bradykinesia and rigidity after deep brain stimulation in a patient with Parkinson disease. Clin Neuropharmacol 2009;32:48-50

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

99. Dhikav V, Anand KS. Acute dystonic reaction with rivastigmine. Int Psychogeriatr 2013;25:1385-6

100. Schneider SA, Bhatia KP. Secondary dystonia-clinical clues and syndromic associations. J Mov Disord 2009;2:58-63

101. Incecik F, Herguner MO, Ozcan K, Altunbasak S. Albendazole-induced dystonic reaction: a case report. Turk J Pediatr 2011;53:709-10

102. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. N Z Med J 1994;107:360-1

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

105. Davis BJ, Aul EA, Granner MA, Rodnitzky RL. Ranitidine-induced cranial dystonia. Clin Neuropharmacol 1994;17:489-91

106. Brashear A, Siemers E. Focal dystonia after chemotherapy: a case series. J Neurooncol 1997;34:163-7

107. Wood N, Pall HS, Williams AC, Dieppe C. Extrapyramidal reactions to anti-inflammatory drugs. J Neurol Neurosurg Psychiatry 1988;51:731-2

108. Iselin-Chaves IA, Grotzsch H, Besson M, et al. Naloxone-responsive acute dystonia and parkinsonism following general anaesthesia. Anaesthesia 2009;64:1359-62

109. Mazurek MF, Rosebush PI. A prospective study of neuroleptic-induced dystonia: incidence and relationship to age, sex, medications and concurrent parkinsonism. Neurology 1991;41:S274

110. Marion MH, Klap P, Perrin A, Cohen M. Stridor and focal laryngeal dystonia. Lancet 1992;339:457-8

111. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;81:463-9

112. Pulce C, Mollon P, Pham E, et al. Acute poisonings with ethyle loflazepate, flunitrazepam, prazepam and triazolam in children. Vet Hum Toxicol 1992;34:141-3

113. Kutt H, Winters W, Scherman R, McDowell F. Diphenylhydantoin and Phenobarbital Toxicity. The Role of Liver Disease. Arch Neurol 1964;11:649-56

114. Shaw SH, Curson H, Coquelin JP. A double-blind, comparative study of zolpidem and placebo in the treatment of insomnia in elderly psychiatric in-patients. J Int Med Res 1992;20:150-61

115. Krach LE. Pharmacotherapy of spasticity: oral medications and intrathecal baclofen. J Child Neurol 2001;16:31-6

116. Zaccara G, Cincotta M, Borgheresi A, Balestrieri F. Adverse motor effects induced by antiepileptic drugs. Epileptic Disord 2004;6:153-68

117. Ghatak NR, Santoso RA, McKinney WM. Cerebellar degeneration following long-term phenytoin therapy. Neurology 1976;26:818-20

118. Hain TC, Cherchi M, Yacovino DA. Bilateral vestibular loss. Semin Neurol 2013;33:195-203

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

120. Lugassy G, Shapira A. A prospective cohort study of the effect of vincristine on audition. Anticancer Drugs 1996;7:525-6

121. Camdessanche JP, Jousserand G, Ferraud K, et al. The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. Brain 2009;132:1723-33

122. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. Neurology 2002;58:1333-7

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

124. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. J Peripher Nerv Syst 2001;6:14-20

125. Brefel-Courbon C, Gardette V, Ory F, Montastruc JL. Drug-induced myoclonus: a French pharmacovigilance database study. Neurophysiol Clin 2006;36:333-6

• An epidemiologic assessment of drug-induced myoclonus.

126. Yoshida K, Moriwaka F, Matsuura T, et al. Myoclonus and seizures in a patient with parkinsonism: induction by levodopa and its confirmation on SEPs. Jpn J Psychiatry Neurol 1993;47:621-5

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

128. Bougea A, Gerakoulis S, Anagnostou E, et al. Donepezil-induced myoclonus in a patient with Alzheimer disease. Ann Pharmacother 2014;48:1659-61

129. Aguglia U, Zappia M, Quattrone A. Carbamazepine-induced nonepileptic myoclonus in a child with benign epilepsy. Epilepsia 1987;28:515-8

130. Wallace EL, Lingle K, Pierce D, Satko S. Amlodipine-induced myoclonus. Am J Med 2009;122:e7

131. Deik AF, Shanker VL. A case of amiodarone-associated myoclonus responsive to levetiracetam. Can J Neurol Sci 2012;39:680-1

132. Lazar A, Mau-Holzmann UA, Kolb H, et al. Multiple organ failure due to 5-fluorouracil chemotherapy in a patient with a rare dihydropyrimidine dehydrogenase gene variant. Onkologie 2004;27:559-62

133. Isitemiz I, Uzman S, Toptas M, et al. Prevention of etomidate-induced myoclonus: which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study. Med Sci Monit 2014;20:262-7

134. Tominaga H, Fukuzako H, Izumi K, et al. Tardive myoclonus. Lancet 1987;1:322

135. Gadow KD, Sverd J, Sprafkin J, et al. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. Arch Gen Psychiatry 1999;56:330-6

136. Alonso-Navarro H, Jimenez-Jimenez FJ. Amisulpride-induced tardive motor and phonic tics. Clin Neuropharmacol 2006;29:163-4

137. Neglia JP, Glaze DG, Zion TE. Tics and vocalizations in children treated with carbamazepine. Pediatrics 1984;73:841-4

138. Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 2011;72:1222-8

139. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20

140. Hoque R, Chesson AL, Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 2010;6:79-83

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

141. Brown LK, Dedrick DL, Doggett JW, Guido PS. Antidepressant medication use and restless legs syndrome in patients presenting with insomnia. Sleep Med 2005;6:443-50

142. Terao T, Terao M, Yoshimura R, Abe K. Restless legs syndrome induced by lithium. Biol Psychiatry 1991;30:1167-70

143. Santamaria J, Iranzo A, Tolosa E. Development of restless legs syndrome after dopaminergic treatment in a patient with periodic leg movements in sleep. Sleep Med 2003;4:153-5

144. Tan EK, Ho SC, Koh L, Pavanni R. An urge to move with L-thyroxine: clinical, biochemical, and polysomnographic correlation. Mov Disord 2004;19:1365-7

145. Kraus T, Schuld A, Pollmacher T. Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol 1999;19:478-9

146. Drake ME. Restless legs with antiepileptic drug therapy. Clin Neurol Neurosurg 1988;90:151-4

147. O'Sullivan RL, Greenberg DB. H2 antagonists, restless leg syndrome, and movement disorders. Psychosomatics 1993;34:530-2

148. Vetrugno R, La Morgia C, D'Angelo R, et al. Augmentation of restless legs syndrome with long-term tramadol treatment. Mov Disord 2007;22:424-7

149. Ware JC, Brown FW, Moorad PJ, et al. Nocturnal myoclonus and tricyclic antidepressants. Sleep Research 1984;13:72

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

151. Louden MB, Morehead MA, Schmidt HS. Activation by selegiline (Eldepryle) of REM sleep behavior disorder in parkinsonism. W V Med J 1995;91:101

152. Iranzo A, Santamaria J. Bisoprolol-induced rapid eye movement sleep behavior disorder. Am J Med 1999;107:390-2

153. Kizilay F, Ekmekci B, Gungor H, et al. Flunarizine-induced fasciculation-myokymia. J Clin Neuromuscul Dis 2011;12:246-7

154. Gangireddy VG, Mitchell LC, Coleman T. Cefepime neurotoxicity despite renal adjusted dosing. Scand J Infect Dis 2011;43:827-9

155. Nicholson D, Scalettar R, Jacobs RP. Rheumatoid rigor: gold induced myokymia. A report and review of the literature. J Rheumatol 1986;13:195-6

156. Teravainen H, Makitie J. Myokymia, unusual side-effect of clofibrate. Lancet 1976;2:1298

157. Tan EK, Chan LL, Lo YL. "Myorhythmia" slow facial tremor from chronic interferon alpha-2a usage. Neurology 2003;61:1302-3

Figure caption

Figure 1. The schematic depiction of the neurochemical aspects of striatal architecture. (5-HT – serotonin, 5-HT_x – serotonin receptor, α_2 – alpha-2 adrenergic receptor, ACh – acetylcholine, AMPA – alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, A_{2A} – adenosine 2a receptor, β_1 – beta-1 adrenergic receptor, δ – 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, κ – kappa opioid receptor, LC – locus coeruleus, LTN – laterodorsal tegmental nucleus, LTS – low-treshold spiking interneuron, μ – 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.

Group	DID	DIT	DIM	DIA	SS	Myoky mia	RBD RSWA	DITi c	Akathisia	NM S	PLMS	Holmes tremor
Antidepressants	+	+	+		+		+	+			+	
Antiepileptics	+	+	+	+	+			+				
Antipsychotics	+	+							+	+		
Antimicrobials	+	+	+	+		+						
Antiemetics	+	+	+						+	+		
Antiarrhythmics		+	+	+			+					
Mood stabilizers		+			+							
Opioids	+		+		+							
Chemotherapeutics	+	+	+	+								
Ca^{2+}-channel blockers	+		+			+						
Antiparkinson			+				+					
Psychostimulants	+	+						+				
Hormones		+										
Benzodiazepines	+		+	+								
VMAT inhibitors		+										
Immunsuppressants		+										
Antihiperlipidemics						+						
Central muscle relaxants				+								
AChE inhibitors	+		+									
H_2 receptor blockers	+											

Table 1. Continued

Group	DID	DIT	DIM	DIA	SS	Myokymia	RBD RSWA	DITic	Akathisia	NMS	PLMS	Holmes tremor
Antihistamines	+											
Anaesthetics	+		+									
Sleeping pills				+								
Antirheumatics						+						
INFα2a inhibitors												+
NSAID	+											
Antimetabolites												
Anticholinergics												
Bronchodilatators		+										
DA synthesis blockers												

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, DIM – Drug-induced myoclonus, DIT – Drug-induced tremor, DITic – Drug-induced tic, H_2 – Histamine-2 receptor, INFα2a – interferon alpha-2a, NMS – Neuroleptic malignant syndrome, NSAID – Non-steroid anti-inflammatory drug, PLMS – Periodic limb movements of sleep, RBD – Rapid eye movement (REM) behavior disorder, RLS – Restless legs syndrome, RSWA – REM sleep without atonia, SS – Serotonine syndrome.