Drug-induced movement disorders

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ABSTRACT

This comprehensive review covers approaches for both the recognition and management of drug-induced movement disorders. Pharmacotherapeutic approaches for treating akathisia, dystonia, Parkinsonism and tardive dyskinesia are explored. The importance of early detection via periodic assessment is discussed.

KEYWORDS

drug-induced movement disorder, akathisia, dystonia, Parkinsonism, tardive dyskinesia

This article will cover the recognition and pharmacotherapeutic approaches for management of drug-induced movement disorders (DIMDs) such as akathisia, dystonia, Parkinsonism, and tardive dyskinesia (TD). Of particular relevance to mental health clinicians is the potential for psychotropics to induce DIMDs (non-psychotropic causative medications will not be discussed in this article).

Comprehensive pharmacotherapy in mental health service involves periodic, consistent monitoring and appropriate communication of side effects. All persons involved in the coordination, delivery, portability, and transparency of clinical care can be edified by a consistent approach in the assessment of side effects. The use of simple checklists incorporating user-friendly, valid, and reliable assessment scales for movement disorders (often available freely in the public domain) can facilitate individual and collaborative practices. At times, the responsible party for implementing or maintaining side effect monitoring may not be clearly defined within the service. If this is the case, pharmacist practitioners can advocate, encourage, and assist in the development of monitoring parameters that are suitable for their mental health service area.

The term "EPS" or extrapyramidal symptom is often used to refer to DIMDs. Whenever, possible, the specific type movement should be communicated / documented (e.g., akathisia, dystonia, Parkinsonism, TD or stereotypy).

PUBLIC / MENTAL HEALTH

Broadly speaking, young males are more susceptible towards developing dystonic reactions, the elderly more prone to drug-induced Parkinsonism, and elderly females more susceptible for developing TD. It is also common for patients to develop two or more co-existing / overlapping DIMDs.

Significant effects of DIMDs include medication nonadherence, reduced quality of life, and increased healthcare utilization. Additionally, DIMDs interfere with social functioning, interpersonal communication, performance of motor tasks, and activities of daily living. In one study, patients with schizophrenia or schizoaffective disorder who developed antipsychotic-induced EPS were 40 times more likely to discontinue maintenance medication.[1]

Psychotropic drugs commonly associated with akathisia, dystonia, Parkinsonism, and TD are listed in Tables 1 to 4.

PRIMARY PREVENTION AND EARLY DETECTION

The necessity of acute or chronic use of conventional neuroleptics should be carefully evaluated. If indicated, the lowest effective dose should be used and patients should undergo regular evaluations for DIMDs (e.g., every 3 to 6 months). Atypical antipsychotics are associated with a reduced risk of DIMDs compared with high-potency neuroleptics (e.g., haloperidol) with or without concurrent antimuscarinic prophylaxis.[2-5] Of note, dose-related EPS is observed with some atypical antipsychotics such as olanzapine, paliperidone, and risperidone.

Early detection is a key factor in the probability of eventual remission of DIMDs. If treatment with a psychotropic (Tables 1-4) has been extended for 3 months or longer, the patient should be periodically examined to determine the presence of early signs of abnormal movements or postures.

PHARMACO-ETIOLOGY

Haloperidol and phenothiazine neuroleptics are drugs commonly associated with various DIMDs. Lithium

treatment commonly induces tremor and occasionally chorea.[6,7] Selective serotonin reuptake inhibitors (SSRIs) commonly induce akathisia and tremor and rarely dyskinesia, dystonia, or Parkinsonism.[8,9] Stimulant drugs (e.g., amphetamine, methylphenidate, pemoline) may occasionally induce a variety of movement disorders such as dyskinesias, dystonia, stereotypies, and tics.[10] Tricyclic antidepressants (TCAs) commonly induce tremor and less frequently myoclonus.[11, 12] The psychotropic antiepileptic agents rarely induce movement disorders, with the exception of valproate, which is commonly associated with tremor and sporadically with Parkinsonism.

Table 1. Psychotropic Agents Associated with Akathisia

Amoxapine	Atypical antipsychotics[a]	Conventional neuroleptics[b]
Lithium	Selective serotonin reuptake inhibitors	Tricyclic antidepressants

[a] clozapine and quetiapine considered low risk
[b] chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, thiothixene, thioridazine, trifluoperazine

Table 2. Psychotropic Agents Associated with Dystonia

Atypical antipsychotics[a]	Conventional neuroleptics

[a] clozapine and quetiapine considered low risk

Table 3. Psychotropic Agents Associated with Parkinsonism

Amoxapine	Atypical antipsychotics[a]
Conventional neuroleptics	Valproate

[a] clozapine and quetiapine considered low risk

Table 4. Psychotropic Agents Associated with Tardive Dyskinesia

Amoxapine
Atypical antipsychotics[a]
Conventional neuroleptics

[a] clozapine and quetiapine considered low risk

The pharmaco-etiology of DIMDs involves blockade of dopaminergic receptors within the striatum. The rate at which a pharmacophore dissociates from dopamine D2 receptors may also contribute. Rapid dissociation from dopamine D2 receptors has been correlated with low EPS potential.[13] According to the dissociation rate hypothesis, atypical antipsychotics bind loosely to dopamine D2 receptors, resulting in a short duration of binding, which is sufficient to produce antipsychotic activity without inducing EPS. Conventional neuroleptics bind tightly to dopamine D2 receptors and thus produce antipsychotic activity but at an increased risk of inducing EPS. Furthermore, among the atypical antipsychotics, rapid dissociation occurs more readily with a low potency agent as opposed to a high potency agent. For example, EPS is rare with clozapine (an agent that requires higher milligram doses for efficacy) compared with risperidone (an agent that requires lower milligram doses). The atypical antipsychotics also block serotonin-2A ($5\text{-}HT_{2A}$) receptors. Serotonin is believed to inhibit synaptic dopamine release and therefore blockade of $5\text{-}HT_{2A}$ receptors has been hypothesized to enhance dopamine release and partially mitigate EPS risk without compromising efficacy.

SYMPTOMATOLOGY

Assessment of abnormal movements involves obtaining a detailed drug and medical history, noting the onset and characteristics of symptoms, and identifying factors associated with symptom aggravation and relief. An attempt to classify the abnormal movement (e.g., as akathisia, dystonia, Parkinsonism, TD or a mixture) is important as the treatment differs for specific types of DIMD. As with idiopathic movement disorders, anxiety and stress will exacerbate DIMD symptoms.

AKATHISIA

Akathisia is most commonly associated with antipsychotics and SSRIs. Of note, treatment emergent anxiety, agitation, and restlessness are often noted with SSRIs and most likely a subset of these patients are experiencing akathisia.

Symptoms of untreated akathisia tend to wax and wane over time, and occasionally will remit. Akathisia can persist for months or years. In addition to treatment non-adherence, akathisia has been associated with promoting aggression and suicidal behavior.[16-18]

Of note, worsening of anxiety and aggressive behavior may result in an increase in antipsychotic dose, which in turn may exacerbate the underlying akathisia. Therefore, it is important to distinguish drug-induced akathisia from agitation/restlessness related to the psychiatric disorder (e.g., agitated depression, dementia).

Akathisia: Clinical Presentation (Table 5)

The Barnes Akathisia Rating Scale may be used for akathisia detection and assessment.[19] Symptoms of acute akathisia typically occur within 4 weeks of initiating or increasing the dose of the offending drug and may also develop after neuroleptic cessation or dose reduction (i.e., withdrawal akathisia). Occasionally, the withdrawal of a concurrent anti-akathisia agent (e.g., antimuscarinic agent, beta blocker) may unmask akathisia. An onset of symptoms after 3 months of stable drug therapy is

Table 5. Signs and Symptoms Associated with DIMDs (adapted from Chen and Swope)[14]

Akathisia	Subjective feeling of restlessness (often in the legs) and need to move. One or more objective symptom such as fidgety movements or leg swinging while seated, marching on the spot while standing, or rocking from one foot to another, pacing to relieve subjective restlessness or an inability to sit or stand still for several minutes.[15] Distress if restrained or unable to move. Symptoms may improve during sleep or in a supine position.
Dystonia	Sustained involuntary muscle contractions or spasms resulting in abnormal postures or twisting and repetitive movements. Affect body parts include the neck, upper and lower extremities, jaw, larynx, and trunk. Symptoms associated with distress, pain, and disability. Difficulty with ambulation, breathing, head turning, speech, and swallowing may occur.
Parkinsonism	Tremor, rigidity, slowness of movement affecting bilateral upper and lower extremities and truncal regions. Masked facies, micrographia, slow shuffling gait, and stooped posture maybe observed.
Tardive Dyskinesia	Abnormal involuntary choreoathetoid movements affecting the orofacial region, tongue, upper and lower extremities, and trunk. Orofacial features include involuntary blinking, chewing and lower jaw movements, grimacing, lip puckering and smacking, tongue protrusion and twisting, and facial tic-like movements. Symptoms are not painful but may result in embarrassment in social settings and difficulty with chewing, speech, and swallowing. Many patients also experience concurrent choreoathetoid or stereotypic movements of the foot, hands, limbs, trunk, head, and neck.

considered tardive. Tardive akathisia can also occur several months after drug withdrawal or dose reduction.

Akathisia: Management[20-31]

Management of drug-induced akathisia consists of:

- Discontinuing or reducing dose of causative agent
- If due to neuroleptic, switching to an atypical antipsychotic
- Trial of antimuscarinic agent (e.g., benztropine, diphenhydramine) or β-blocker (i.e., propranolol)
- Trial of miscellaneous agents (e.g. amantadine, benzodiazepine, clonidine, cyproheptadine, mianserin, mirtazapine, trazodone).

In a patient at high risk for akathisia (e.g., prior history of akathisia), concurrent administration of an antimuscarinic agent or β-blocker is reasonable.

In cases in which the offending drug is discontinued, the akathisia may resolve only to be replaced with increased agitation and anxiety. Care should be taken to differentiate this from persistent akathisia. Administration of a lipophilic β-blocker, such as propranolol, is effective and well tolerated. Although the β_1-receptor blockers are less effective, a trial is reasonable if β_2-blockade is undesirable. The hydrophilic β-blockers, e.g., atenolol and nadolol, do not appear to be effective. Administration of antimuscarinic agents, benzodiazepines, or antiserotonergic agents (cyproheptadine) are also effective and may be preferred if a sedative effect is desired. Less commonly used agents are also listed previously.

Although iron deficiency has been associated with acute and tardive akathisia, routine iron supplementation as a preventative or treatment intervention is not supported by the available evidence.[32] Regardless, if there is an existing underlying iron deficiency, iron supplementation should be administered.

DYSTONIA (ACUTE AND TARDIVE)

Dystonia: Clinical Presentation (Table 5)

Acute dystonia can occur within hours to several days of initial exposure to a neuroleptic or less commonly after a dosage increase or a reduction in concomitant antimuscarinic agent. Symptoms include sustained postures, which can be focal or generalized. The severity of symptoms and anatomic distribution varies but the classic clinical presentation is characterized by the three O's: oculogyric crisis (conjugate deviation of the eyes upward or laterally), opisthotonos or extensor axial dystonia (involuntary posturing in which the head, neck, and spine are arched backward), and oromandibular dystonia (forceful contractions of the jaw causing difficulty in opening or closing the mouth). Blepharospasm (involuntary eyelid closure), jaw-closing dystonia, laryngeal spasm, tongue protrusion, and respiratory stridor may be also be present. Symptoms are usually painful and can interfere with ambulation, breathing, speaking, swallowing, and vision.

Rhabdomyolysis may occur. In severe cases (e.g., laryngeal spasm), acute dystonia can be life threatening.

Neuroleptic malignant syndrome (NMS) should be considered if dystonia occurs in the presence of neuroleptic exposure, fever, generalized rigidity, altered level of consciousness, and autonomic instability. In some cases, NMS is difficult to distinguish from serotonin syndrome (key differentiating features are that serotonin syndrome requires exposure to a serotonergic agent such as an SSRI and the presence of myoclonus).

Tardive dystonia develops after months to years during treatment with an antipsychotic or within 3 months after discontinuation. Remission of tardive dystonia is uncommon. The severity of the abnormal posturing may vary from mild to severe, pain may or may not be present, and a dystonic head tremor may be present. Pisa syndrome is a rare form of dystonia that is most commonly associated with neuroleptic treatment and characterized by sustained truncal lateroflexion.[33]

DRUG-INDUCED DYSTONIA: MANAGEMENT

Management of acute dystonia consists of:

- Discontinuing the offending agent
- Administering an antimuscarinic agent (e.g., benztropine, diphenhydramine) administered orally, intramuscularly, or intravenously
- Benzodiazepines may be administered in conjunction with an antimuscarinic

Management of tardive dystonia consists of:

- Withdrawal or dosage reduction of offending agent
- If due to neuroleptic - switching to an atypical antipsychotic
- Trial of antimuscarinic agent
- Management of concurrent anxiety
- Botulinum toxin injection (for focal dystonias)
- Trial of benzodiazepine
- Trial of muscle relaxant (e.g., baclofen, oral or intrathecal)
- Trial of dopamine-depleting agents (e.g., tetrabenazine)
- Less commonly used drugs include amantadine, β-blockers, benzodiazepines, clonidine, dantrolene, levodopa, and antiepileptics such as levetiracetam, pregabalin, tiagabine, and zonisamide
- For medically refractory cases, deep brain stimulation (globus pallidus) or pallidotomy

Because the greatest risk of neuroleptic-induced dystonia occurs within the first week of treatment, the short-term administration of oral antimuscarinic agents may be considered, especially in patients receiving high-potency antipsychotics.[34-36] The efficacy of antimuscarinic prophylaxis appears to be inversely related to age of the patient (in other words, antimuscarinic prophylaxis appears to be less effective in older patients).[37] Although advocated by some clinicians, long term prophylaxis (in EPS naïve patients) with an antimuscarinic is controversial.

DRUG-INDUCED PARKINSONISM (DIP)

In addition the antipsychotics, other psychotropic drugs that can induce Parkinsonism include α-methyldopa, reserpine, and valproate. Valproate-induced Parkinsonism is characterized by concurrent cognitive and hearing impairments and is under-recognized.[38] Although SSRI-induced tremor is common, SSRI-induced DIP is rare.

DRUG-INDUCED PARKINSONISM: CLINICAL PRESENTATION (TABLE 5)

In mental health, the Simpson-Angus Scale can be used to detect and assess for DIP. Clinical features of DIP are indistinguishable from idiopathic Parkinsonism and include at least two of the following features: tremor (rest or postural), rigidity, and bradykinesia. In the absence of an accurate drug history, symptoms of DIP can be easily mistaken for idiopathic PD. Sometimes, classic DIP is characterized by symmetrical distribution of symptoms and a low-frequency, high-amplitude chin or jaw tremor.[39] In the majority of cases, DIP remits upon drug withdrawal; but complete resolution often takes up to 6 months or longer; and some patients never have the DIP fully resolve.

DRUG-INDUCED PARKINSONISM: MANAGEMENT

Management of DIP consists of:

- Withdrawal or dosage reduction of offending agent
- If due to neuroleptic - switch to an atypical antipsychotic
- Trial of antimuscarinic, amantadine, dopamine agonist, or levodopa

Although there is disagreement among clinicians, antimuscarinic agents are used for primary prophylaxis of DIP.

TARDIVE DYSKINESIA (TD)

Tardive dyskinesia develops after at least 1-month exposure to the offending agent. Generally speaking, a patient's risk of TD is greatest during the initial 5 years of

neuroleptic treatment. Elderly patients are approximately 5 times more likely to develop TD when compared to younger adults.[40]

Tardive dyskinesia can result in social impairment and isolation, employment difficulties, and stigmatization. In some cases, functional impairment occurs (e.g., difficulties with chewing, speaking, and swallowing). Orofacial dyskinesias may also result in dental problems, denture displacement, and damage to the soft tissues within the oral cavity.

Tardive Dyskinesia: Clinical Presentation (Table 5)

The Abnormal Involuntary Movement Scale (AIMS) is a commonly employed instrument for assessing, monitoring, and screening.[41] This scale rates dyskinetic movements in seven body regions and includes assessments for global severity, functional impairment, and self-awareness of symptomatology. Mild symptoms generally go unnoticed by patients. Factors associated with exacerbation of TD include administration of antimuscarinics or sympathomimetic stimulants and emotional extremes. Symptoms of TD can be suppressed for brief periods of time. Distraction during voluntary movements of unaffected body parts (e.g., finger tapping test) or during performance of mental tasks (e.g., arithmetic) will unmask latent dyskinesia in other body parts. As with most dyskinesias, symptoms subside during sleep.

Remission rates are low if the offending agent is not discontinued. Early detection is imperative, as remission rates are inversely correlated with duration of TD. Occasionally, withdrawal emergent TD may occur. This describes TD that develops due to withdrawal of antipsychotic treatment and is observed in pediatric mental health.[42-43] Generally, withdrawal emergent dyskinesia improves within 3 months. Also, latent TD may be "unmasked" during a reduction in neuroleptic dose or during a switch from a conventional to an atypical antipsychotic. When assessing TD symptoms, symptoms should not be mistaken for the orofacial ***dyskinesia-like*** movements that are very common in edentulous individuals.

Rabbit syndrome is an uncommon subtype of TD that involves a slow, rhythmic, vertical-only tremor of the perioral region that resembles the chewing motions of a rabbit. Rabbit syndrome is very specific to the buccal region only and differs from orofacial TD in that tongue involvement is absent. Some clinicians consider rabbit syndrome as a form of drug-induced Parkinsonism. Treatment involves reduction of neuroleptic dosage as much as possible or a trial of an antimuscarinic agent. This contrasts with orofacial TD in which addition of an antimuscarinic tends to exacerbate the symptoms.

Tardive Dyskinesia: Management

Management of TD consists of:

- Withdrawal or dosage reduction of offending agent
- Withdrawal of concurrent antimuscarinic agents
- If due to neuroleptic - switch to an atypical antipsychotic
- If withdrawal dyskinesia is suspected, reintroduce the offending agent and initiate a slow taper and then discontinue.
- Manage concurrent anxiety (e.g., with benzodiazepines)
- Botulinum toxin (focal dyskinesias)
- Trial of vitamin E
- Trial of tetrabenazine
- Less commonly used agents include amantadine, baclofen, branched chain amino acids, calcium channel blockers (e.g., diltiazem, nifedipine, verapamil), donepezil, gabapentin, levetiracetam, melatonin, methyldopa, ondansetron, pregabalin, and pyridoxine (Vitamin B6).
- Deep brain stimulation (globus pallidus) or pallidotomy for severe medically refractory cases

Overall, treatments for TD have proven to be disappointing and efficacy is inconsistent. The practice of intermittent antipsychotic treatment (or drug holidays) is not beneficial for TD and has been found to be associated with an increased risk of TD and also higher rates of psychosis relapse and rehospitalization.[44,45] Paradoxically, increasing the neuroleptic dosage sometimes suppresses the dyskinesias but this approach is considered by many to be inappropriate. The various treatment approaches are listed previously. Vitamin E 1600 international units/day may be more beneficial in patients with TD for less than 5 years.[46,47]

CONCLUDING REMARKS

Drug-induced movement disorders are a mental health concern. Periodic monitoring for movement disorders is a component of comprehensive mental health care. At times, the responsible party for implementing or maintaining side effect monitoring may not be clearly defined within the service. If this is the case, pharmacist practitioners can advocate, encourage, and assist in the development or coordination of monitoring that is suitable for their mental health service area.

As an additional note, before initiating antipsychotics, mental health clinicians should consider informing patients regarding the potential risk of DIMDs.[48] The discussion concerning the risk of movement disorders should take place after the patient has been stabilized from acute psychiatric features and if anticipated treatment will be for greater than 3 months.[49] Educating and involving patients and caregivers can facilitate early detection and reporting of drug-induced movement disorders.

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