

# DRUG-INDUCED MOVEMENT DISORDER EMERGENCIES

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## Introduction

Movement disorders as a subspecialty comprises the syndrome of parkinsonism, a variety of involuntary movements, ataxia and muscle stiffness/hyperexcitability syndromes. Involuntary movements include tremor, myoclonus, chorea and dystonia. While the processes underlying these disorders is generally chronic and evaluated within the outpatient clinic, there are situations in which the disorders may present acutely or subacutely and present within a hospital practice or emergency room. In such cases, drug-induced movement disorders are often a likely cause. This presentation will review several well-recognized drug-induced movement disorders.

## Approach to Movement Disorders

Movement disorders evaluation starts with the visual categorization of the motor phenomena. Parkinsonism is a syndrome or resting tremor, bradykinesia, rigidity and a typical stooped, shuffling gait and/or loss of postural control. Tremor is a rhythmic movement of a body part(s) at a constant frequency. Myoclonus is a rapid, simple movement of one joint or it may simultaneously involve multiple joints. Chorea comprises more complex, multiple joint movements varying randomly in their timing and appearance. Dystonia is sustained muscle contraction creating an abnormal joint position. Dystonia can be phasic, causing the same posture in a repetitive movement or tonic causing a fixed posture.

Once a movement disorder is categorized a diagnosis is reached based on time course of onset, further clinical and family history and diagnostic tests. Drug-induced movement disorders will generally have an acute or subacute onset. Most importantly, a drug-induced movement disorder will abate with withdrawal of the offending agent.

## Drug-induced Parkinsonism

Parkinson's disease and atypical Parkinsonian syndromes have an insidious onset and a slowly progressive course over years. Parkinsonism presently acutely is rare. Acute Parkinsonism would suggest a drug-induced, vascular, or infectious cause.

Drug-induced Parkinsonism (DID) was described by Hall et al in 1956 during initial observations of chlorpromazine in which signs of Parkinsonism were recorded in 40% of patients.<sup>1</sup> DID is common worldwide representing at least 20% of Parkinsonism cases.<sup>2,3</sup> Age and female gender are the strongest risk factors.<sup>4</sup> First generation anti-psychotics such as chlorpromazine, haloperidol and perphenazine have a high incidence of DID. Atypical antipsychotics such as olanzapine, risperidone, and quetiapine have a lower incidence of DID, but still pose a significant risk. Quetiapine is the safest in the elderly. Aripiprazole was said to be a novel partial D2 agonist as well as antagonist that would protect from DID, but in fact it has reported DID side effects. Only clozapine, a novel D4 receptor blocker, is not associated with Parkinsonism, but requires hematologic monitoring. Anti-emetics such as metoclopramide and prochlorperazine, both D2 antagonists are the second class of agents highly associated with DID. Other drugs implicated in DID at a low level of incident risk include SSRIs, calcium channel blockers, reserpine, tetrabenazine, lithium, sodium valproate and others.<sup>5,6</sup>

The question often arises as to whether a patient has drug-induced Parkinsonism, idiopathic Parkinsonism or a combination of the two. Clinical observations pointing toward DID include the co-existence of tardive dyskinesia, severe postural tremor and a synchronous (as opposed to alternating) agonist/antagonist firing pattern on EMG testing.<sup>6,7</sup> If diagnosis is still unclear, our approach is to withdraw the suspected medicine and re-examine for

resolution of Parkinsonian signs. For dopamine blocking drugs 6 months or longer may be required for complete resolution of symptoms.<sup>8</sup> If signs persist at 6 months we generally perform an loflupane I<sup>123</sup> scan (DAT scan). A normal DAT scan will demonstrate the absence of nigrostriatal neurodegeneration in DID.<sup>9</sup>

The use of levodopa or dopamine agonists in drug-induced Parkinsonism is controversial. Initial studies indicated an absence of response, although anecdotal reports suggest a partial response.<sup>10,11</sup>

### **Acute Dystonic Reactions**

Dystonia occurring acutely or subacutely is most commonly due to drugs. Other considerations are vascular events, encephalitis, paraneoplastic disorders (CRMP-5, ANNA-2) and rapid-onset dystonia-Parkinsonism (DYT-12). Drug induced dystonia was recognized early in the use of chlorpromazine and studies initially focused on post-synaptic dopamine receptor hypersensitivity.<sup>12</sup> However, recent studies implicate sigma receptors.<sup>13</sup> With neuroleptics, dystonia can occur with initial exposure, after prolonged exposure (tardive) or after discontinuation of the agent (withdrawal emergent). Regardless of the timing of drug exposure, the presentation of dystonia can be acute or subacute. First generation antipsychotics have a high rate of dystonic or dyskinesic reactions (estimate 32%). Atypical anti-psychotics have reduced the incidence of such reactions. Risperidone reduced the risk of dyskinesia/dystonia by 75% compared to haloperidol. Olanzapine likely better, and quetiapine better still. Clozapine poses no or negligible risk for dyskinesia/dystonia.<sup>14</sup> Other medications inducing acute dystonia include anti-emetics such as metoclopramide, sodium valproate, rivastigmine, anti-convulsants, tetrabenazine, and others.

*Oculogyric crises* presents as sustained conjugate upgaze. It is often associated with facial grimacing, jaw opening and other craniocervical dystonias.<sup>15</sup> Oculogyric crises can be caused by a variety of neurologic diseases, but drugs cause two-thirds of cases, usually during the first exposure. *Pharyngeal dystonia* is a rare dystonic reaction involving spasms of pharyngeal and laryngeal muscles that can result in respiratory compromise requiring emergency airway management.<sup>16</sup> *Tardive dystonia* describes a dystonic phenotype in which patients are incapacitated by severe neck and axial spasms causing dramatic backwards deviation of neck and trunk.<sup>17</sup> This is usually a chronic syndrome but could present in the emergency room given the severity of the posture. *Pisa syndrome* describes a truncal dystonia with a lateral, twisting bend.<sup>18</sup>

Treatment of acute dystonic reactions in the emergency room aims at stabilization of the movements with medication. Diphenhydramine 25-50 mg intravenous or anticholinergic medications such as benztropine 1-2 mg intramuscular or intravenous are used for rapid control of movements and generally work within minutes. Withdrawal of the offending medication generally relieves the dystonia long term, but the patient should be discharged on follow-up anticholinergic treatment for at least a week. For tardive dystonia, where the movement disorder may become chronic, botulinum toxin therapy or pallidal deep brain stimulation has been used.

### **Akathisia**

Akathisia represents a behavioral syndrome in which a patient feels a strong compulsion to move. Patients pace, rock, walk in place or move their legs aware of the compulsion, but unable suppress it. Unlike restless legs syndrome, the compulsion is not accompanied by a sense of pain or sensory phenomenon. Akathisia may be caused by the same drugs that induce acute dystonia and is more prevalent than dyskinesia in patients. Atypical antipsychotics have a much lower incidence of akathisia.<sup>19</sup> In a community study, 18.5% of treated schizophrenics reported some degree of akathisia.<sup>20</sup> The compulsion to move generally abates with drug withdrawal. However, if drug therapy needs to be continued treatment with quetiapine carries the lowest risk of akathisia. Propranolol or anticholinergic medications may also be of benefit.

### **Status dystonicus**

Status dystonicus or “dystonic storm” is a rare condition first described by Jankovic and Penn.<sup>21</sup> Patients have a known generalized dystonic condition that acutely worsens and manifests continual, severe generalized dystonia. The condition is often life threatening with respiratory compromise, pneumonia, rhabdomyolysis and multiorgan failure.<sup>22</sup> Factors triggering status dystonicus include infection, fever, general anesthesia or drugs. Drugs implicated include anti-psychotics, anti-emetics, penicillamine and zinc. Changes in drug therapy for the underlying dystonia can also trigger status dystonicus. No standard treatment has been found effective although immediate treatment with midazolam and propofol has been advocated.<sup>23</sup> Attempts are then made to stabilize the

maintenance drug therapy that may include anticholinergics, tetrabenazine and other agents. If the severe dystonia persists intrathecal baclofen or deep brain stimulation has been reported to have success in individual cases.<sup>24</sup>

## Tremor

Drug-induced tremor is an extremely common phenomenon arising from a wide range of medications.<sup>25</sup> However, the difficulties in reports of drug-induced tremor include a lack of information about pre-existing tremor and lack of documentation of the severity of tremor. Most drug-induced tremors are believed to arise from augmentation of peripheral reflex arcs causing exaggerated physiologic tremor. In our experience only a few agents cause *severe postural tremor* causing disability. Drugs such as lithium, sodium valproate, amiodarone, overdose with thyroxine and the anti-rejection drugs fall into this category.<sup>26,27</sup> A large number of medications frequently cause a mild, fine, rapid postural tremor that results in little impact on activities of daily living. SSRI's, tricyclic antidepressants, beta-agonist inhalers, corticosteroids and acyclovir fall into this latter category.

## Myoclonus

Myoclonus caused by drugs is generally multifocal and associated with encephalopathy as in the serotonin syndrome or beta-lactam induced encephalopathy. In the hospital drugs and anoxia (Lance-Adams syndrome) are the major causes of acute myoclonus. Drugs associated with acute myoclonus include opioids used for post-operative pain control, especially meperidine.<sup>28</sup> Other medications include anti-psychotics, SSRIs, gabapentin, pregabalin, lithium and antibiotics other than beta-lactam class agents such as trimethoprim-sulfamethoxazole and hydroxyquinolones.<sup>29</sup>

## Chorea

Acute or subacute chorea is generally caused by inflammatory conditions such as anti-phospholipid antibody syndrome, SLE or paraneoplastic disorders (CRMP-5 antibody or NMDA encephalitis). Chorea caused by drugs is rare and can be seen with the initiation of oral contraceptives or other estrogen containing medications.<sup>30</sup> Other medications associated with chorea are baclofen, lithium, gabapentin, valproate and memantine. Illegal drugs especially crack cocaine induce chorea through the sudden and massive release of dopamine. This results in choreoathetotic movements termed "crack dancing".<sup>31</sup>

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