Drug-Induced Movement Disorders: Emergencies and Management

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Movement disorders often have an insidious onset and slow progression, and are not often associated with emergency situations. However, neurologists may be called on to diagnose and treat evolving movement disorders or acute complications of existing diseases in the emergency room or intensive care unit. Such situations meet the working definition of an “emergency,” a rapidly evolving disorder (hours to days) in which the failure to diagnose and treat may lead to significant morbidity or mortality.1 Because the key to diagnosis in movement disorders is recognition, key features that help to distinguish each movement disorder are presented in Table 1. This article discusses rapidly evolving situations that may require emergency intervention. Several of the disorders discussed are rare, so treatment guidelines are often not based on randomized, double-blind, placebo-controlled trials.

NEUROLEPTIC MALIGNEANT SYNDROME

Neuroleptic malignant syndrome (NMS), first described in 1960,2 is an iatrogenic disorder resulting from exposure to drugs that block dopamine receptors. Although most cases are caused by neuroleptics (both typical and atypical, even clozapine),3–6 other medications such as prochlorperazine, metoclopramide, amoxapine, tetrabenazine, droperidal, lithium, and promethazine are also implicated.7–11 Diagnostic criteria...
integrating clinical and laboratory features (Table 2) have been developed. Newer consensus guidelines that include expert opinion from psychiatrists, neurologists, anesthesiologists, and emergency medicine specialists are in development. Because the incidence of NMS is low (0.2%), a high index of suspicion is necessary to make the appropriate diagnosis. NMS is important to consider in any patient with acute-onset parkinsonism and fever because it is life threatening (mortality rate 5%–20%). Young and middle-aged men appear to be at higher risk. Postpartum women may also have an elevated risk. Case reports of identical twins with NMS suggest that there may be genetic susceptibility as well.

NMS is a clinical syndrome comprising fever, rigidity, mental status change, autonomic dysfunction, and other movement disorders (tremor, dystonia, and myoclonus). Key laboratory abnormalities include leukocytosis and elevated creatine phosphokinase. In addition, acute-phase reactants including albumin and serum iron are decreased. Symptoms often begin after initiation or an increase in neuroleptic dose. NMS increases in severity over 48 to 72 hours and lasts 2 to 14 days. Medical

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical definitions of movement disorders</th>
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<tr>
<td>Myoclonus</td>
<td>Sudden, brief, shocklike movements</td>
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<td>May be due to muscle contraction (positive myoclonus) or loss of muscle tone (negative myoclonus or asterixis)</td>
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<tr>
<td>Dystonia</td>
<td>Involuntary sustained muscle contractions that produce twisting or squeezing movements</td>
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<td>Often accompanied by abnormal posture</td>
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<tr>
<td>Parkinsonism</td>
<td>Cardinal features include bradykinesia, rigidity, tremor, and postural instability</td>
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<td>All features need not be present</td>
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<tr>
<td></td>
<td>Drug-induced parkinsonism is often symmetric and may lack tremor</td>
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<tr>
<td>Tremor</td>
<td>Rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles</td>
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<tr>
<td>Tics</td>
<td>Brief, paroxysmal movements or vocalizations sometimes accompanied by premonitory urge</td>
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<td></td>
<td>May be stereotyped</td>
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<tr>
<td></td>
<td>Unlike other hyperkinetic movements, may be voluntarily suppressed for a short period of time</td>
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<tr>
<td>Chorea</td>
<td>Involuntary, irregular, purposeless movements that “flow” into one another in a random fashion</td>
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<td>Rapid, large-amplitude proximal movements that are sometimes described as “flinging,” are referred to as ballism, and represent an extreme end of the spectrum of chorea</td>
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<th>Table 2</th>
<th>Diagnostic criteria for NMS</th>
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<tr>
<td>Criteria</td>
<td>Feature</td>
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<tr>
<td>Major</td>
<td>Fever, rigidity, elevated creatine phosphokinase level</td>
</tr>
<tr>
<td>Minor</td>
<td>Tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, leukocytosis</td>
</tr>
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The presence of all 3 major, or 2 major and 4 minor criteria, indicates a high likelihood of NMS in the appropriate clinical context.
complications can be chronic and irreversible and include renal failure from rhabdomyolysis, respiratory failure from decreased chest wall compliance, aspiration pneumonia, and other complications of immobility such as deep venous thrombosis and pressure ulcers. Pulmonary embolism, pneumonia, or renal failure may result in death.

No prospective, randomized trials exist for NMS. Key steps in treatment include withdrawal of the causative agent and treatment with dopaminergic agents. Bromocriptine has been used most often and is considered the drug of choice; however, other dopaminergic agents including carbidopa/levodopa, ropinirole, and pramipexole are likely effective. Dantrolene, a nonspecific muscle relaxant, reduces muscular rigidity and minimizes rhabdomyolysis if the dopaminergic agent does not reverse the symptoms. Combination therapy has been found to be safe and effective, and treatment should continue for 7 to 10 days depending on the half-life of the causative agent. One-third of patients may relapse if neuroleptics are restarted too early, so waiting at least 2 weeks after NMS has cleared is good practice. In patients who require acute treatment of psychosis, electroconvulsive therapy has been successful.

PARKINSONISM-HYPERPYREXIA SYNDROME

Parkinsonism-hyperpyrexia syndrome (PHS) may be indistinguishable from NMS except that it occurs in patients with preexisting parkinsonism. PHS occurs in patients with Parkinson disease (PD) who abruptly withdraw or reduce dopaminergic medications. It was first reported in the context of abrupt discontinuation of antiparkinsonian medications during “levodopa holidays” in the 1980s. Although levodopa holidays are no longer recommended, patient noncompliance or abrupt changes in medication replicate that scenario. Aggressive medication adjustments are not uncommon, particularly after deep brain stimulation surgery (DBS) in PD. Clinicians must realize that PHS is a potential complication and that DBS does not protect the patient from PHS. Although abrupt withdrawal of first-line antiparkinsonian medication (carbidopa/levodopa and dopamine agonists) is the typical scenario for PHS, discontinuation of amantadine or tolcapone has also been reported as causative. Rapidly switching between dopamine agonists may also lead to PHS. Dehydration and metabolic disturbances may also precipitate it. Treatment involves supportive measures and reinstituting dopaminergic therapy. Bromocriptine and dantrolene may be added as additional therapy. High-dose intravenous methylprednisolone has been proposed as adjunctive therapy, and appears to be effective based on one small, randomized trial. Despite treatment, permanent worsening of PD and fatalities have been reported.

SEROTONIN SYNDROME

Any drug that enhances serotonergic transmission can precipitate serotonin syndrome (SS), which has the core clinical features of fever, myoclonus, and altered mental status. SS was first described in 1960 in patients receiving monoamine oxidase inhibitor (MAO-I) monotherapy, but is now encountered in patients taking 2 or more drugs with serotonergic actions (tricyclic antidepressants or selective serotonin reuptake inhibitors [SSRI] in combination with nonselective MAO-I) (Box 1). Although selective MAO-B inhibitors (rasagiline, selegiline) do carry a warning regarding their use in combination with SSRIs, the agents are routinely used together in PD patients with only rare reports of SS occurring. An underrecognized causative agent of SS is fentanyl, a widely used anesthetic that is a direct serotonin agonist. When used in patients taking SSRIs, it has the potential to cause SS. Many of
the clinical features overlap with NMS; however, SS may have additional clinical features such as myoclonus, hyperreflexia, seizures, and mood alteration (restlessness, elevated mood). This overlap may relate to the impact that elevated serotonin levels have on lowering dopamine levels. Treatment consists of discontinuation of the causative agent, supportive therapy, and cyproheptadine for severe cases. Cyproheptadine, an antihistamine and serotonin antagonist, is given in divided doses up to a maximum dose of 32 mg/d. SS may resolve quickly or can be fatal. Two case reports have been published detailing the use of electroconvulsive therapy for the treatment of refractory SS. As with NMS and PHS, the rarity and seriousness of SS precludes large, randomized trials.

**ACUTE DYSTONIC REACTION**

Acute dystonic reaction is most commonly seen after exposure to dopamine receptor blockers, both neuroleptics and antiemetics. Dystonia begins within 24 hours of exposure, and 90% of reactions occur within 5 days. Acute dystonic reactions are less common than tardive dyskinesia or drug-induced parkinsonism, affecting approximately 6% of patients exposed to “typical” neuroleptics and 1% to 2% of those exposed to “atypical” neuroleptics. Clinical manifestations are diverse, usually affecting the head and neck. Laryngeal dystonia, blepharospasm, cervical dystonia, oculogyric crisis, and focal limb dystonia have all been reported. Acute dystonic reactions are more common in young men, whereas tardive dyskinesia and drug-induced parkinsonism are more common in the elderly. Concomitant alcohol abuse may increase the risk of developing acute dystonic reactions and akathisia. Treatment with an intravenous anticholinergic agent such as benztropine (1–2 mg) or with diphenhydramine (25–50 mg) is very effective. Because of the possibility of a reoccurrence, a short oral course of an anticholinergic (4–7 days) may be necessary. After an acute dystonic reaction, patients are at higher risk for future dystonic reactions when exposed to other dopamine receptor blockers.

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**Box 1**

Drugs reported to cause serotonin syndrome

- Monoamine oxidase inhibitors
- Selective serotonin reuptake inhibitors
- Serotonin and norepinephrine reuptake inhibitors
- Tricyclic antidepressants
- 5-Hydroxytryptophan
- Buspirone
- Opiates (except morphine)
- Lithium
- Triptans
- 3,4-Methylenedioxyamphetamine (ecstasy)
- Lysergic acid diethylamide (LSD)
- Amphetamines
- Cocaine
Cocaine and amphetamines both enhance neurotransmission of monoamines (dopamine, norepinephrine, and serotonin). Cocaine blocks neurotransmitter reuptake at the synaptic nerve endings while amphetamines increase release of neurotransmitters from synaptic nerve endings. Chronic use of these psychostimulants can lead to stereotypic motor behaviors, tics, dystonia, chorea, and myoclonus. Amphetamine use is highly associated with punding behaviors (complex prolonged, purposeless, and stereotyped behavior), while chorea is well described in cocaine users (“crack dancing”). Abnormal movements usually appear during intoxication, they may persist for days or weeks, and have been described during withdrawal. In patients with tic disorders, psychostimulants have the potential to lead to an acute worsening; this has not been proved in a randomized treatment trial of methylphenidate in children with attention-deficit/hyperactivity disorder and tic disorders. No specific treatment is available for neurologic complications of psychostimulant toxicity.

### 3,4-METHYLENEDIOXYMETHAMPHETAMINE

3,4-Methylenedioxymethamphetamine, or ecstasy, is a “designer drug” that has effects similar to those of psychostimulants and hallucinogens. Side effects can include a variety of neurologic symptoms including anxiety, tremor, ataxia, rigidity, myoclonus, and nystagmus. Of importance, ecstasy may also cause seizures and malignant hyperthermia. It should be considered in the differential diagnosis of both NMS and SS. The mechanism of hyperthermia in ecstasy overdose may be attributable to massive serotonin release, and there are many similarities to the

<table>
<thead>
<tr>
<th>Movement Disorder</th>
<th>Medication Class</th>
<th>Medication</th>
<th>Initial Daily Dose (mg)</th>
<th>Recommended Maximum Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea</td>
<td>Neuroleptic</td>
<td>Haloperidol</td>
<td>0.5</td>
<td>8</td>
</tr>
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<td></td>
<td>Risperidone</td>
<td>0.5</td>
<td>6</td>
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<tr>
<td></td>
<td>Tetrabenazine</td>
<td>12.5</td>
<td>75</td>
<td></td>
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<tr>
<td></td>
<td>Dopamine-depleting agent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clonazepam</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine</td>
<td></td>
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<tr>
<td></td>
<td>Anticonvulsant</td>
<td>Valproic acid</td>
<td>750</td>
<td>Titrate to serum level</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
<td>500</td>
<td>3000</td>
<td></td>
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<tr>
<td></td>
<td>Primidone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.5</td>
<td>750</td>
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</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>0.5</td>
<td>6</td>
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</tr>
<tr>
<td>Myoclonus</td>
<td>Anticonvulsant</td>
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</tr>
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<td>Tics</td>
<td>Neuroleptic</td>
<td>Haloperidol</td>
<td>0.5</td>
<td>8</td>
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<tr>
<td></td>
<td>Dopamine-depleting agent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clonazepam</td>
<td>0.5</td>
<td>6</td>
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<tr>
<td></td>
<td>Antihypertensive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clonidine</td>
<td>0.1</td>
<td>0.6</td>
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<tr>
<td></td>
<td>Guanfacine</td>
<td>1</td>
<td>3</td>
<td></td>
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<tr>
<td>Acute dystonic reaction</td>
<td>Anticholinergic</td>
<td>Benztropine</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>25</td>
<td>400</td>
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</tbody>
</table>

<sup>a</sup> These agents are generally not helpful in acute treatment but can be given with a neuroleptic that could eventually be discontinued.
symptoms seen in classic SS as well as NMS. Treatment is generally supportive, though aggressive measures should be taken to prevent extreme hyperthermia. In case reports, dantrolene has been effective in the treatment of ecstasy overdose complicated by hyperthermia (>40°C).

**OPIOIDS**

Opioids are prescribed commonly for the treatment of pain, but are also frequently abused. When used at typical doses, opioids may cause myoclonus and reduce the seizure threshold. One prescription opioid, meperidine, has a much higher likelihood of adverse neurologic effects and is of particular interest. Meperidine may cause a variety of neuropsychiatric adverse effects including agitation, delirium, hallucinations, seizure, tremor, and myoclonus. In addition, meperidine may contribute to the development of SS in patients taking tricyclic antidepressants, SSRIs, or serotonin and norepinephrine reuptake inhibitors.

**MOTOR FLUCTUATIONS AND DYSKINESIA IN PARKINSON DISEASE**

Motor fluctuations are common in advanced PD, seen in 40% of patients by 4 to 6 years with an increasing frequency of 10% per year. Generally not dangerous, motor fluctuations are one of the more common disease-specific reasons for which patients seek emergency treatment. During “off” periods, prominent rigidity, bradykinesia, and postural instability may develop, making it impossible for the patients to care for themselves or to walk. Psychiatric features may become pronounced, including depressed mood, anxiety, and, panic. Dysautonomia including tachycardia, diaphoresis, and variations in blood pressure may occur. While “off” periods do not usually result in a visit to the emergency department, some situations lead to emergency evaluation. Patients with suddenly worsening “off” periods associated with new symptoms (eg, freezing, unpredictable, or prolonged “off” periods) are more likely to seek urgent evaluation. In these situations investigation should search for a potential cause of the abrupt change. A careful compilation of medication history is necessary to ensure that no changes have been made to the antiparkinsonian regimen. Patients should also be questioned about the addition of medications to their regimen, particularly dopamine receptor blockers (antipsychotics and antiemetics), as exposure to dopamine receptor antagonists may lead to abrupt deterioration in PD. Concurrent infection (urinary tract infection, pneumonia) or metabolic derangement should be considered. In a patient with falls and abruptly worsening PD, subdural hematoma should be considered.

Levodopa-induced dyskinesia (LID) is usually not dangerous and is most often managed in the outpatient setting. However, severe LID may lead to rhabdomyolysis and dehydration. Generalized LID may be complicated by involvement of respiratory muscles, with patients reporting symptoms of dyspnea, tachypnea, chest wall discomfort, and involuntary grunting. Failure to recognize respiratory dyskinesia may lead to unnecessary testing. Greater emphasis on medical and medication history may improve the diagnosis of respiratory dyskinesia in the emergency setting. Treatment of dyskinesia should include lowering (or holding) levodopa dosage. Benzodiazepines may be useful to treat concomitant anxiety. Neuroleptics should not be used. Long-term management for chronic dyskinesia may involve the addition of amantadine or DBS.

**PSYCHOSIS IN PARKINSON DISEASE**

Psychosis in PD is a common reason for inpatient admission and is a strong predictor of nursing home placement. It is more commonly encountered in PD with dementia.
(PDD), occurring in 45% to 64% of patients.\textsuperscript{82,83} Visual hallucinations are more common than auditory hallucinations, and usually consist of complex, formed visual images, often of unknown but nonthreatening people.\textsuperscript{84} Paranoid delusions may accompany hallucinations, and constitute a greater problem. Hallucinations and mild delusions may be treated at home, but paranoia may become extreme and require hospitalization. PD psychosis may be precipitated by metabolic derangements, infections (urinary tract infection, pneumonia), and changes in drug therapy, including addition of any dopaminergics or anticholinergics.

Emergency treatment of psychosis requires a multifaceted approach. The patient’s living conditions need to be assessed to determine whether hospitalization is required. A thorough workup for metabolic or infectious disorders is indicated. Nonessential psychoactive medications should be discontinued. Dopaminergic drugs that are least potent with respect to motor function should be reduced (anticholinergics, amantadine, dopamine agonists, MAO-B inhibitors, catechol-O-methyltransferase inhibitors).\textsuperscript{85} The daily levodopa dose may also need to be lowered. An antipsychotic medication can be started, and is often necessary to resolve psychosis. Useful antipsychotics include clozapine and quetiapine. Clozapine has the most robust evidence base.\textsuperscript{86} Despite the lack of compelling evidence for quetiapine,\textsuperscript{86} it is often prescribed because of clozapine’s risk of agranulocytosis and the need for monitoring the complete blood count on a frequent basis. Other antipsychotics, “typical” and “atypical,” may cause unacceptable worsening of motor function and should not be used for treatment of psychosis in PD.\textsuperscript{85,86}

**ACUTE PARKINSONISM**

Acute or subacute onset of parkinsonism has a broad differential diagnosis. Parkinsonism as part of a primary neurodegenerative disease is insidious in onset and slowly progressive. However, when parkinsonism develops over a period of days to weeks, a secondary cause should be considered. In this situation a review of the medication list, investigation for a structural lesion, and examination for pathognomonic findings are most important. In the absence of a structural abnormality, particular attention should be given to potential medication or toxic exposures (Table 4).\textsuperscript{87}

While neuroleptics (typical and atypical) and dopamine-blocking antiemetics (especially metoclopramide) are widely recognized in causing parkinsonism, other medication classes and occupational toxins have also been implicated.

<table>
<thead>
<tr>
<th>Iatrogenic and toxic causes of acute parkinsonism</th>
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<tbody>
<tr>
<td>Drug-induced</td>
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SUMMARY

Although movement disorders are often not regarded as emergencies, there will be situations when the neurologist will be called upon to consult emergently. A common etiology in movement disorders emergencies is that of a toxic exposure, to either prescription or illicit drugs. The workup should always include a careful record of medication and drug history. Because these cases are rare, consulting a neurologist is advisable. This article has reviewed the diagnosis and management of acute-onset movement disorders occurring secondary to drug use, drug withdrawal syndromes, and drug-induced emergencies occurring in patients with movement disorders. These disorders are uncommon and few in any randomized controlled trials that have been conducted. When possible, treatment recommendations are made based on randomized trial data; however, due to the uncommon nature of the disorders, clinical experience and literature reports form the basis for many treatment recommendations.

REFERENCES

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