Movement Disorders: Overview and Treatment Options

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Educational Objectives

- Review the terminology used to describe movement disorders.
- Discuss individual movement disorder syndromes, including essential tremor, Parkinson’s disease, dystonia, myoclonus, chorea, tic disorders, tardive dyskinesia, akathisia, restless limbs syndrome, and Wilson’s disease.
- Review current treatment options for individual movement disorders.

Introduction

The area of movement disorders is a subspecialty of neurology focusing on a variety of conditions that are characterized by hypokinetic, hyperkinetic, or abnormally coordinated movements. These conditions include tremor, parkinsonism, dystonia, myoclonus, chorea, ballismus, ataxia, tic disorders, dyskinesia, akathisia, restless limbs, and others. The term “movement disorders” may be used to refer to either abnormal movements or to syndromes that cause these abnormal movements.

The classification of movement disorders is based on phenomenology, individual syndromes, or etiology. In this article, we will first review the terminology used to describe movement disorders, then briefly discuss individual movement disorder syndromes. The focus of this article is on treatment options.

Terminology

A tremor is a rhythmic oscillation of a body part by alternating or synchronous contraction of agonist and antagonist muscles. Usually, the hands are involved, but the head, jaw, voice, tongue, and the lower limbs may also be affected.

A resting tremor occurs while a limb is not active or when it is at complete rest against gravity. The resting tremor in Parkinson’s disease (PD) affects the upper limbs asymmetrically.

An action tremor, such as that seen in essential tremor (the most common movement disorder), can be:

- postural, as when a limb maintains position against gravity (e.g., with the hands in the outstretched position).
- intention (terminal), as observed in the finger-to-nose-to-finger test.
- task-specific (observed while a person is performing a certain activity, such as writing).

Parkinsonism is a nonspecific term that refers to a combination of signs seen in PD. These include tremor, rigidity, bradykinesia, and postural instability. PD is defined more specifically, with gradations of diagnostic certainty (Table 1).

Dystonia is an abnormal sustained muscle contraction causing twisting or turning around one or multiple joints. It may affect the neck (cervical dystonia or torticollis), eyelids (blepharospasm), limbs, trunk, or vocal cords (spasmodic dysphonia). Dystonia can be focal, segmental, or generalized. “Writer’s cramp” is a focal hand dystonia. With segmental dystonia, an entire limb or trunk is involved. Generalized or multifocal dystonia affects multiple body parts.

Myoclonus may be “positive” or “negative.” Positive myoclonus is a sudden, brief muscle contraction; a negative myoclonus (e.g., asterixis) is an interruption of muscle contraction in the extended arm and wrist that causes inhibition of the activated muscle.

Chorea, meaning “dance” in Greek, resembles exaggerated fidgetiness. The movements are usually generalized and purposeless. In mild cases, chorea may be blended into natural movements and may appear purposeful.

Choreoathetosis refers to slow and writhing movements. Ballismus is a large-amplitude, sometimes violent, proximal chorea. It usually occurs acutely on one side of the body (hemiballismus) after an infarct in the contralateral subthala-
mic nucleus (STN) or with STN stimulation for the treatment of PD.

Ataxia refers to impaired motor coordination that is usually related to disorders of the cerebellum or its connections with the brain and spinal cord. It is characterized by slurred speech, nystagmus, dysmetria (undershooting or overshooting a target with trajectory limb movements), poor dexterity, and a wide-based gait. There are no proven drug treatments for ataxia caused by primary degenerative cerebellar syndromes. The therapy for secondary ataxia syndromes (e.g., toxic/metallic, drug-induced, paraneoplastic, or Wilson’s disease) would involve treatment of the primary condition.

Tics are temporarily suppressible, abnormal movements or vocalizations. Simple motor tics are isolated, brief, sudden movements that involve one body part. Complex motor tics may involve more than one body part and may have a component of dystonia, other complex movements, or even obscene gestures (copropraxia). A simple vocal tic may be a grunt or a throat clearing. Complex vocal tics are more elaborate vocalizations, words or phrases, even profanity (coprolalia).

Dyskinesia literally means “abnormal movement.” However, the term has evolved to refer to abnormal drug-induced involuntary movements, usually choreatic, dystonic, or a combination of both. Dyskinesia in PD patients results from the long-term complications of levodopa therapy. Tardive dyskinesia refers to choreodystonic movements secondary to the long-term use of neuroleptic or antiemetic medications that have dopamine antagonist activity.

Akathisia is excessive motor activity that is intended to relieve a sensation of inner restlessness, which occurs either acutely or as a late complication of neuroleptic medications. Patients display agitation, with an inability to remain seated, and are usually shifting their weight, or pacing.

Restless limbs syndrome occurs as a distressing desire to move the limbs (usually the legs) while sitting or lying down. The disorder is relieved by walking. Symptoms worsen in the evening, and periodic limb movements may occur during sleep.

### Treatment of Movement Disorder Syndromes

#### Essential Tremor

Essential tremor is a prevalent movement disorder. The tremor is present during action, and the hands, head, and voice are affected to variable degrees. A family history is positive in most patients, with a dominant inheritance pattern and variable penetrance. The occurrence of a family history is more common if the patient’s relatives are examined. Tremors are worsened by caffeine, stress, and associated medical disorders, such as hyperthyroidism, and they are relieved by alcohol.

#### Medical Therapy

The initial medication for essential tremor is usually either primidone (Mysoline®, Xcel) or propranolol (e.g., Inderal®, Wyeth). The starting dose of primidone is 50 mg at bedtime, with the doses gradually increasing up to 750 mg daily. Side effects include somnolence, fatigue, cognitive problems, and ataxia. Propranolol should be started at 10 mg daily and titrated as tolerated to 320 mg daily. Adverse drug effects (ADEs) include bradycardia, hypotension, fatigue, bronchospasm, depression, and impotence.

Primidone and propranolol can be administered together. Topiramate (Topamax®, Ortho-McNeil), gabapentin (Neurontin®, Pfizer), and the benzodiazepines (e.g., diazepam [Valium®, Roche]) may also relieve tremors. Injections of botulinum toxin may also be helpful.

#### Surgical Options

**Thalamotomy**

When severe essential tremor is intractable to medical therapy, unilateral thalamotomy (surgical destruction of a small part of the thalamus) improves the contralateral tremor. Bilateral thalamotomy is rarely performed, because it can result in cognition and gait disturbances.

**Deep-Brain Stimulation**

Although the exact mechanism of deep-brain stimulation is unknown, the technique is thought to suppress neuronal activity in the target (in this case, the same part of the thalamus that would be destroyed in thalamotomy) by stimulating it at high frequency. Thalamic deep-brain stimulation is considered safer...
than thalamotomy, presumably because there is no significant destruction of brain tissue, the effects are considered reversible, and the degree to which the target is suppressed can be adjusted.

Serious surgical complications include symptomatic brain hemorrhage (usually fewer than 3% of patients) and death (fewer than 1%).

**Parkinson’s Disease**

The cardinal features of PD are resting tremor, rigidity, and bradykinesia. Postural instability is sometimes considered a cardinal feature, but this is a nonspecific finding that is usually absent in early PD, especially in younger patients. Nonmotor features may occur in PD, including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms, and sleep disturbances. The diagnostic criteria for PD have become more rigorous with gradations of diagnostic certainty (Table 1). The prevalence of PD in industrialized countries is estimated at 0.3% of the general population; approximately 1% of people over 60 years of age are affected. The prevalence is slightly higher in men than in women. The mean age of onset is about 60 years, but 5% of patients experience their first symptom before age 40.

The etiologic mechanism of PD is unknown, but aging, environmental factors, and a genetic predisposition probably all play a role. The recent discovery of several genetic loci related to familial PD has led to the hypothesis that failure of the ubiquitin–proteasome system and protein misfolding are the final common pathways in the pathogenesis of PD.

**Medical Therapy**

There is no unequivocal neuroprotective agent currently available for PD. Vitamin E was not beneficial in a large multicenter trial in patients with early PD. The efficacy of selegiline (Eldepryl®, Watson), a monoamine oxidase-B (MAO-B) inhibitor, in delaying the initiation of levodopa is at least partially a consequence of symptomatic relief of motor symptoms rather than neuroprotection.

Patients with early PD who were treated for a year with rasagiline (Teva Pharmaceuticals), another MAO-B inhibitor, showed less functional decline than patients whose treatment with rasagiline was delayed for six months. The issue of possible neuroprotection by MAO-B inhibitors remains unresolved.

One pilot study suggested that high-dose coenzyme Q10 might slow symptom progression in early PD. These results have yet to be confirmed in larger studies with longer follow-up periods.

Controlled trials of dopamine agonists versus levodopa in early PD using functional imaging of the dopaminergic system have claimed a slower rate of disease progression in PD patients who were started on dopamine agonists. However, these results are still being debated, in part because of issues surrounding the accuracy of functional neuroimaging techniques as markers of disease progression.

In a controlled trial of intraventricular infusion of glial cell line–derived neurotrophic factor (GDNF) in PD patients, GDNF did not improve motor symptoms. In an open-label study, five PD patients who received GDNF infusions via catheters directly into the putamen improved after a year. A larger controlled trial of bilateral intraputamenal GDNF infusion sought to confirm these findings, but no benefits over placebo were observed.

Treatment is initiated when motor symptoms cause disability. Anticholinergic agents are rarely used in younger patients, in whom tremor is the major symptom. The more definitive treatment of early PD consists of either a dopamine agonist or levodopa. Because dopamine agonists cause less dyskinesia than levodopa, they are usually the initial therapy for younger patients. Side effects of dopamine agonists include nausea, hypotension, leg edema, vivid dreams, hallucinations (especially in elderly people with cognitive deficits), somnolence, and sleep attacks.

Dopamine agonists have less antiparkinson efficacy than levodopa does, but agonist monotherapy can sometimes control motor symptoms for the first two to five years. The non-ergot agonists, such as pramipexole (Mirapex®, Pfizer) and ropinirole (Requip®, GlaxoSmithKline) may help to prevent rare ergot-related retroperitoneal, pulmonary, and cardiac valve fibrosis.

Levodopa remains the most potent antiparkinson drug and is the backbone of therapy throughout much of the course of the disease. It is the preferred initial drug in older adults and in those with cognitive deficits or serious comorbid conditions. Levodopa is combined with carbidopa (e.g., Sinemet®, Bristol-Myers Squibb) or benserazide (e.g., Parlopa® in Canada) to prevent peripheral conversion to dopamine by dopa-decarboxylase.

Side effects of levodopa are similar to those of dopamine agonists, although somnolence, hallucinations, and leg edema are less common. Complications of long-term levodopa therapy include motor fluctuations, including “end-of-dose wearing-off” and “on–off” phenomena, and dyskinesia. Dividing protein intake throughout the day may help to reduce motor fluctuations.

Controlled-release forms of levodopa may provide a longer duration of benefit, but their absorption is more unpredictable than immediate-release levodopa. Catechol-O-methyl transferase (COMT) inhibitors, such as entacapone (Comtan®, Novartis) and tolcapone (Tasmar®, Roche), prolong the half-life of circulating levodopa and improve end-of-dose wearing-off. Tolcapone is more potent, but its use has declined significantly because of a few cases of fatal liver failure. Dyskinesia can be alleviated with a lower levodopa dosage but at the expense of worsening motor symptoms. In patients with motor fluctuations and dyskinesia, adding a dopamine agonist to levodopa may help reduce motor fluctuations. It may also allow for levodopa reduction, which can turn alleviates dyskinesia.

The subcutaneously injectable dopamine agonist apomorphine is useful for rapid treatment of “off” periods in PD. However, given the severity of apomorphine-induced nausea,
Premedication with domperidone (Motilium®), or trimethobenzamide (Tigan®, King) is needed. Amantadine (Symmetrel®, Endo) may also suppress dyskinesia, possibly by N-methyl-D-aspartate (NMDA) receptor antagonism.43

Nonmotor Symptoms

Nonmotor symptoms in PD may occur as part of the disease or as complications of treatment. These include depression, constipation, sleep disturbance, psychosis, cognitive impairment, orthostatic hypotension, drooling, and urinary urgency. Depression in PD is usually treated with a selective serotonin reuptake inhibitor (SSRI).44 No controlled head-to-head studies have suggested that one SSRI is superior to another in PD. The aggressive use of multiple modalities (e.g., stool softeners, increased fiber intake, and suppositories) is indicated for treating constipation.

Disorders of sleep in PD patients include daytime somnolence, sleep attacks, night-time awakenings caused by overnight bradykinesia, rapid-eye movement (REM) behavior disorder, and restless limbs or periodic limb movements.45 Daytime somnolence and sleep attacks may be associated with dopamine agonists, and the agonist may have to be discontinued.46

Overnight bradykinesia and restless limbs syndrome may be alleviated with a bedtime dose of long-acting levodopa, sometimes with entacapone, or a dopamine agonist. Clonazepam (Klonopin®, Roche) is effective in treating REM behavior disorder.

Psychosis in PD patients is thought to be mostly drug-induced, and it occurs more frequently in patients with dementia. Dopamine agonists are more likely than levodopa to cause hallucinations.38

First, the agonist or anticholinergic agent should be discontinued, and the lowest dose of levodopa should be used. Adding an atypical neuroleptic drug may be necessary. Quetiapine fumarate (Seroquel®, AstraZeneca) is the more popular atypical neuroleptic agent in therapy for PD. It causes fewer extrapyramidal ADEs than risperidone (Risperdal®, Janssen) or olanzapine (Zyprexa®, Eli Lilly), and there is no need for weekly or biweekly measurements of the complete blood count (CBC), as would be required with clozapine (Clozaril®, Novartis).47 Open-label studies have suggested that dementia and psychosis in PD may be treated with central cholinesterase inhibitors.48

Rivastigmine tartrate (Exelon®, Novartis) has been effective for dementia with Lewy bodies49 and in treating the dementia associated with PD.50 Another small randomized, controlled study showed that donepezil (Aricept®, Esai/Pfizer) improved cognition in PD patients.51 Memantine (Namenda®, Forest), proven to be effective in moderate-to-severe Alzheimer’s dementia,52 has not been evaluated in a large, controlled study for dementia in PD, but it may prove to be useful.

Treatment options for hypotension include reducing the dosage of antiparkinson medications, increasing the salt and fluid intake, and adding fludrocortisone acetate (Florinef®, King) or midodrine (ProAmatine®, Shire). Drooling may be reduced by the peripheral anticholinergic agent glycopyrrolate (Robinul®, First Horizon), but this drug may worsen constipation. Injection of botulinum toxin into the salivary glands reduces drooling.53

Urinary urgency may be treated with peripheral anticholinergic agents, such as oxybutynin (Ditropan®, Ortho-McNeil) and tolterodine tartrate (Detrol®, Pfizer) or with alpha-adrenergic blocking agents, such as prazosin (Minipress®, Pfizer) and terazosin (Hytrin®, Abbott). Unfortunately, the former agents worsen constipation and the latter agents exacerbate hypotension.

Surgical Options

Deep-Brain Stimulation

For more than a decade, deep-brain stimulation of "hyperactive" nuclei has been used to help relieve motor symptoms in PD patients with severe motor fluctuations and dyskinesia. High-frequency stimulation of deep-brain targets presumably reduces neural activity in the tissue surrounding the electrode contact.

The suppression of the target induced by this technique can be sculpted by adjustments of the electrode configuration, stimulation intensity, pulse width, and frequency. Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) helps to relieve PD motor symptoms.54 Some researchers claim that bilateral STN stimulation is superior to bilateral GPi stimulation in PD patients because it allows a reduction in antiparkinson medications,55 but the debate continues regarding the optimal stimulation target for PD. A large randomized, multicenter study comparing bilateral STN to bilateral GPi stimulation is currently under way.

The adverse effects of deep-brain stimulation include brain hemorrhage, infarct, seizures, and death. Other complications include breakage of the leads, various hardware failures, malfunction of the pulse generator, and infected hardware. Side effects from the stimulation itself include gait disturbances and worsening dyskinesia, paresthesias, cognition, mood, and speech. The stimulation-related side effects may be reversible by adjusting stimulation parameters.

The key to a successful outcome is appropriate patient selection.56 Surgical patients must have clinically definitive PD with documented motor improvement after levodopa therapy. All attempts to optimize drug therapy must have failed to relieve motor fluctuations or dyskinesia. Patients should not have dementia, untreated psychiatric conditions, or serious medical illnesses. Dedication and commitment from patients and their families are essential for maintaining frequent follow-up visits.

Restorative (Transplantation) Therapy

In the first randomized sham surgery-controlled study of fetal mesencephalic tissue transplantation, younger patients showed some improvement in the "medication-off" state, but many patients experienced disabling dyskinesia.57 The second randomized, controlled study found no significant motor improvement.58 Most transplant recipients developed dyskinesia.

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td>Propranolol (beta blocker)</td>
<td>30–180 mg daily</td>
<td>Hypotension, bradycardia, fatigue, impotence, bronchospasm, depression</td>
</tr>
<tr>
<td></td>
<td>Primidone (anticonvulsant)</td>
<td>50–500 mg daily</td>
<td>Somnolence, cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Topiramate (anticonvulsant)</td>
<td>25–200 mg daily</td>
<td>Somnolence, cognitive impairment, weight loss, paresthesias</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Immediate-release carbidopa/levodopa (levodopa is a precursor to dopamine, and carbidopa blocks conversion of levodopa to dopamine in the periphery)</td>
<td>25/100 or 25/250 from 1/2 tablet t.i.d. to as high as tolerated, depending on motor symptoms</td>
<td>Nausea, somnolence, dyskinesia, hypotension, hallucinations</td>
</tr>
<tr>
<td>(motor symptoms)</td>
<td>Controlled-release carbidopa/levodopa</td>
<td>25/100 and 50/200 1/2 tablet t.i.d. to as high as tolerated</td>
<td>Nausea, somnolence, dyskinesia, hypotension, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Ropinirole (non–ergot-derived dopamine agonist)</td>
<td>0.25 mg t.i.d. to 5 mg q.i.d.</td>
<td>Nausea, more somnolence than levodopa, less dyskinesia than levodopa, sleep attacks, leg edema, hallucination, hypotension</td>
</tr>
<tr>
<td></td>
<td>Pramipexole (non–ergot-derived dopamine agonist)</td>
<td>0.125 mg t.i.d.–1.5 mg q.i.d.</td>
<td>Nausea, more somnolence than levodopa, less dyskinesia than levodopa, sleep attacks, leg edema, hallucination, hypotension</td>
</tr>
<tr>
<td></td>
<td>Pergolide (ergot-derived dopamine agonist)</td>
<td>0.05 mg t.i.d.–1 mg q.i.d.</td>
<td>Same as ropinirole and pramipexole, plus cardiac valve, retroperitoneal and pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Entacapone (catechol-O-methyl transferase inhibitor)</td>
<td>200 mg with each dose of carbidopa/levodopa</td>
<td>Exacerbates levodopa’s side effects; diarrhea and bright-orange urine</td>
</tr>
<tr>
<td></td>
<td>Tolcapone (catechol-O-methyl transferase inhibitor)</td>
<td>100 mg t.i.d.</td>
<td>Exacerbates levodopa’s side effects; diarrhea, rare liver failure (liver enzyme monitoring required)</td>
</tr>
<tr>
<td></td>
<td>Selegiline (selective monoamine oxidase-B inhibitor)</td>
<td>5 mg b.i.d.</td>
<td>Nausea, insomnia, interaction with other monoamine oxidase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Trihexyphenidyl (central anticholinergic agent)</td>
<td>2–10 mg daily</td>
<td>Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Amantadine (N-methyl-D-aspartate receptor inhibitor)</td>
<td>100 mg b.i.d.–t.i.d.</td>
<td>Nausea, hypotension, hallucinations, confusion, edema</td>
</tr>
<tr>
<td></td>
<td>Apomorphine (non–ergot-derived injectable dopamine agonist)</td>
<td>1–6 mg SQ injection for severe “off” episodes</td>
<td>Severe nausea, abdominal cramps, yawning, somnolence, hallucinations, hypotension</td>
</tr>
</tbody>
</table>

**Parkinson disease**  
* (non-motor symptoms)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM behavior disorder</td>
<td>Clonazepam (benzodiazepine)</td>
<td>0.25–3 mg</td>
<td>Residual daytime somnolence, impaired cognition, worsening of sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Quetiapine (antipsychotic agent)</td>
<td>12.5–200 mg daily</td>
<td>Somnolence, worsening of motor symptoms, confusion</td>
</tr>
<tr>
<td></td>
<td>Clozapine (antipsychotic agent)</td>
<td>12.5–100 mg daily</td>
<td>Same as quetiapine plus possible agranulocytosis requiring frequent blood count measurements</td>
</tr>
<tr>
<td>Condition</td>
<td>Medication</td>
<td>Dose Range</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-----------------------------------</td>
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</tr>
<tr>
<td>Dementia</td>
<td>Rivastigmine (central cholinesterase inhibitor)</td>
<td>1.5–6 mg b.i.d.</td>
<td>Nausea and abdominal cramps</td>
</tr>
<tr>
<td></td>
<td>Donepezil (central cholinesterase inhibitor)</td>
<td>5–10 mg daily</td>
<td>Nausea and abdominal cramps</td>
</tr>
<tr>
<td></td>
<td>Galantamine (central cholinesterase inhibitor)</td>
<td>4–12 mg b.i.d.</td>
<td>Nausea and abdominal cramps</td>
</tr>
<tr>
<td>Levodopa- and dopamine agonist-induced nausea</td>
<td>Domperidone (peripheral dopamine antagonist)</td>
<td>10–20 mg with each dose of carbidopa/levodopa or dopamine agonist</td>
<td>No common side effects</td>
</tr>
<tr>
<td>Levodopa-induced nausea</td>
<td>Carbidopa alone (Lodosyn®)</td>
<td>25 mg with each dose of carbidopa/levodopa</td>
<td>No common side effects</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs</td>
<td>Depends on drug</td>
<td>SSRI adverse effects vary among individual drugs</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Fludrocortisone (mineralocorticoid)</td>
<td>0.1–0.3 mg daily</td>
<td>Hypertension, edema, fluid retention</td>
</tr>
<tr>
<td></td>
<td>Midodrine (peripheral alpha-agonist)</td>
<td>10–30 mg daily</td>
<td>Hypertension, piloerection, urinary retention</td>
</tr>
<tr>
<td>Drooling</td>
<td>Glycopyrrolate (peripheral anticholinergic agent)</td>
<td>2–8 mg daily</td>
<td>Dry mouth, dry eyes, constipation, hypotension, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin injections</td>
<td>20–100 units</td>
<td>Dry mouth, difficulty chewing or swallowing</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>Peripheral anticholinergic agents (e.g., tolterodine, oxybutynin)</td>
<td>Depends on drug</td>
<td>Dry mouth, dry eyes, constipation, hypotension, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Alpha-adrenergic blocking agents (e.g., prazosin, terazosin)</td>
<td>Depends on drug</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Trihexyphenidyl</td>
<td>2–10 mg daily</td>
<td>Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Benztropine (central anticholinergic agent)</td>
<td>2–8 mg daily</td>
<td>Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Carbidopa/levodopa</td>
<td>Smaller doses than for Parkinson’s disease</td>
<td>Nausea, somnolence, dyskinesia, hypotension, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin injections for focal dystonia</td>
<td>Depends on body part injected</td>
<td>Depends on body part injected</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Valproic acid (anticonvulsant)</td>
<td>500–2,000 mg daily</td>
<td>Somnolence, cognitive impairment, tremor, hair loss, weight gain, thrombocytopenia, elevated ammonia</td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>1–4 mg daily</td>
<td>Somnolence, cognitive impairment, fatigue</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam (anticonvulsant)</td>
<td>500–3,000 mg daily</td>
<td>Somnolence, cognitive impairment, fatigue</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>50–500 mg daily</td>
<td>Somnolence, cognitive impairment, fatigue</td>
</tr>
</tbody>
</table>
### Table 2  Drug Therapy for Movement Disorders, continued

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chorea</strong></td>
<td>Neuroleptic (antipsychotic) agents</td>
<td>Depends on drug</td>
<td>Somnolence, cognitive impairment, parkinsonism, plus others</td>
</tr>
<tr>
<td></td>
<td>Reserpine (monoamine depleter)</td>
<td>0.1–1.0 mg daily</td>
<td>Hypotension, depression, parkinsonism</td>
</tr>
<tr>
<td></td>
<td>Tetrabenazine (monoamine vesicular transporter inhibitor)</td>
<td>12.5–100 mg daily</td>
<td>Hypotension, depression, parkinsonism</td>
</tr>
<tr>
<td><strong>Tic disorder</strong></td>
<td>Clonidine (central alpha-adrenergic agonist)</td>
<td>0.1–0.4 mg daily</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Neuroleptic agents (quetiapine, risperidone, olanzapine, pimozide, haloperidol)</td>
<td>Depends on drug</td>
<td>Somnolence, cognitive impairment, dystonic reaction, parkinsonism, tardive dyskinesia</td>
</tr>
<tr>
<td></td>
<td>Reserpine and tetrabenazine</td>
<td>Depends on drug</td>
<td>Hypotension, depression, parkinsonism</td>
</tr>
<tr>
<td><strong>Tardive dyskinesia</strong></td>
<td>Stop the offending drug first</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonic dyskinesia only</td>
<td>Trihexyphenidyl or benztropine</td>
<td>Depends on drug</td>
<td>Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Clozapine or quetiapine</td>
<td>Depends on drug</td>
<td>Somnolence, confusion, and agranulocytosis with clozapine</td>
</tr>
<tr>
<td></td>
<td>Reserpine or tetrabenazine</td>
<td>Depends on drug</td>
<td>Hypotension, depression, parkinsonism</td>
</tr>
<tr>
<td><strong>Akathisia</strong></td>
<td>Stop the offending drug first</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No definitive drug therapy (see text)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Restless limbs</strong></td>
<td>Ropinirole</td>
<td>0.25–3 mg qhs, or more often</td>
<td>Nausea, somnolence, leg edema, hypotension, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>0.125–1.5 mg qhs, or more often</td>
<td>Nausea, somnolence, leg edema, hypotension, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Controlled-release carbidopa/levodopa</td>
<td>50/200 1/2 tablet qhs, or more often</td>
<td>Nausea, hypotension, somnolence</td>
</tr>
<tr>
<td></td>
<td>Gabapentin (anticonvulsant)</td>
<td>300–600 mg qhs or more often</td>
<td>Somnolence, cognitive impairment, fatigue</td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>0.25 mg–1 mg qhs or more often</td>
<td>Somnolence, cognitive impairment, fatigue</td>
</tr>
<tr>
<td><strong>Wilson’s disease</strong></td>
<td>Zinc acetate (blocks copper absorption)</td>
<td>50 mg t.i.d.</td>
<td>Gastrointestinal upset and rarely pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Trientene (heavy metal chelator)</td>
<td>250 mg t.i.d. or q.i.d.</td>
<td>Initial neurological worsening, bone marrow suppression, proteinuria, dermatitis</td>
</tr>
<tr>
<td></td>
<td>Penicillamine (heavy metal chelator)</td>
<td>250 mg t.i.d. or q.i.d.</td>
<td>Similar to trientene</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; q.i.d. = four times daily; mg = milligrams; qhs = at bedtime; REM = rapid-eye movement; SQ = subcutaneous; SSRI = selective serotonin reuptake inhibitor; t.i.d. = three times daily.
that persisted after the withdrawal of dopaminergic therapy. Therefore, at present, fetal nigral transplantation is not a treatment option for PD. The negative results from fetal tissue transplantation have dampened the enthusiasm for stem-cell therapy. At present, there are no large-scale stem-cell human clinical trials for PD.

Other Movement Disorders

Dystonia

Dystonia may be classified by the body part affected or by its etiology, including genetic forms. Dopa-responsive dystonia is a rare genetic disorder that begins in childhood. Dystonia usually starts in one leg. There is a diurnal fluctuation, and patients respond dramatically to relatively low doses of levodopa.

Drug-induced dystonia may occur acutely or as a tardive phenomenon from exposure to neuroleptic agents, antiemetic therapy, and promotility drugs with dopamine antagonist activity, such as prochlorperazine (Compazine®, GlaxoSmith Kline), promethazine (Phenergan®, Wyeth) and metoclopramide (Reglan®, Wyeth). Patients must avoid the offending drug and similar drugs in the future, and they should use centrally acting anticholinergic agents, such as benzotropine mesylate (Cogentin®, Merck) orally or intravenously.

Although focal dystonias may be treated initially with anticholinergic agents, benzodiazepines, or muscle relaxants, these drugs are somewhat ineffective at doses that would not cause side effects. Therefore, botulinum toxin injections are the first line of therapy for most focal dystonias, including torticollis, blepharospasm, and focal limb dystonia. In selected cases, electromyographic guidance helps to localize the muscles targeted for injection.

Treatment of generalized dystonia is more challenging, because botulinum toxin cannot be injected at high doses in multiple body parts. Anticholinergic agents, benzodiazepines, muscle relaxants, and anticonvulsants are frequently used.

Other options for managing severe generalized dystonia include intrathecal baclofen (Lioresal®, Novartis), 61 tetra-muscle relaxants, and anticonvulsants are frequently used. Benzodiazepines, benzodiazepines, or muscle relaxants, and anticonvulsants are frequently used. Other options for managing severe generalized dystonia include intrathecal baclofen (Lioresal®, Novartis), clonazepam, and primidone. Levetiracetam (Keppra®, UCB Pharma) has emerged as an effective anticonvulsant drug, and it may also alleviate negative myoclonus, which has traditionally proved challenging to treat.

Chorea

Chorea can be observed in patients with Huntington’s disease, benign hereditary chorea, endocrine-mediated disorders (e.g., hyperthyroidism), or autoimmune-mediated disorders (e.g., Sydenham’s chorea and lupus). Chorea is a major component of levodopa-induced dyskinesia in PD and neuroleptic-induced tardive dyskinesia.

Therapy for chorea begins with treating the underlying condition or reducing or stopping the drug that is potentially causing it. The next step depends on the cause.

In PD patients with levodopa-induced choreic dyskinesia, drug adjustments are necessary (see “Medical Therapy” on page 230).

In neuroleptic-induced choreic tardive dyskinesia, the offending neuroleptic agent should be discontinued. If the patient requires antipsychotic therapy, an atypical neuroleptic agent should be used. Clozapine has proved the most efficacious among the neuroleptic drugs in alleviating tardive dyskinesia; however, it may cause agranulocytosis, and CBC monitoring is necessary.

Anticholinergic medications are not effective in alleviating chorea. In Huntington disease, treatment of chorea begins with a neuroleptic agent, but monoamine-depleting agents may also be used. Benzodiazepines may help suppress chorea in a variety of disorders.

Ballismus, a condition in which the limbs fling violently and involuntarily, is rare. It usually occurs as hemiballismus, with only one side affected, after an infarct in the contralateral STN. The violent nature of ballismus dissipates over time, and the movements become choreatic. Its treatment is similar to that for chorea.

Tic Disorders

Tourette syndrome is a neuropsychiatric disorder characterized by motor and vocal tics. Depression and obsessive-compulsive traits are common in Tourette syndrome and in tic disorders in general. Therefore, treating the underlying psychiatric conditions is extremely important in conjunction with treating the movement disorder.

Two classes of drugs are usually used as first-line therapy to suppress tics: alpha2-adrenergic agonists and neuroleptic agents. Guanfacine (Tenex®, A. H. Robbins) and clonidine (Catapres®, Boehringer Ingelheim) are two alpha2-adrenergic agonists that are less effective than neuroleptic drugs in suppressing tics, but they have better side-effect profiles. Clonidine is commonly used in the U.S. with a starting dose of 0.1
Tardive Dyskinesia and Akathisia

Tardive dyskinesia is typically choreatic, dystonic, or a combination of the two. It is usually a late complication of neuroleptic therapy, but it may occur rarely after repeated exposure to promotility or antiemetic agents that have dopamine antagonist activity.68 Of course, it is best to prevent tardive syndromes by using the lowest dose of an atypical antipsychotic agent for the shortest possible duration.

Once tardive dyskinesia is present, its treatment can be challenging. The data supporting the use of vitamin E and benzodiazepines are weak, although the sedative and anxiolytic effects of the benzodiazepines may suppress abnormal movements.

There are no large-scale head-to-head studies comparing atypical neuroleptic agents among themselves. Clozapine and quetiapine are associated with the lowest reported cases of tardive dyskinesia.69 Therefore, the offending neuroleptic agent should first be stopped. If the patient requires neuroleptic treatment, quetiapine should be tried initially. However, if psychosis prevails or tardive dyskinesia deteriorates, clozapine therapy with CBC monitoring may be necessary.

Centrally acting anticholinergic drugs, such as benzotropine or trihexyphenidyl (Artane®, Lederle) may alleviate dystonic dyskinesia, but they do little for choreatic dyskinesia. Monoamine-depleting agents may also be used in intractable cases of tardive dyskinesia.62

Neuroleptic-induced akathisia is characterized by dysphoria and motor restlessness.8 Treatment of akathisia begins with discontinuation of the offending neuroleptic agent. If the patient requires neuroleptic therapy, using the lowest dose of an atypical antipsychotic agent, preferably quetiapine, is recommended. A number of drugs, including beta blockers, anticholinergics, clonidine, amantadine, and even opiates, have been somewhat successful in alleviating akathisia.

Restless Limbs Syndrome

Restless limbs syndrome is a common disorder with a prevalence of 5% to 15% in Western countries.9 It is characterized by a distressing desire to move the legs, with motor restlessness brought on by rest. Symptoms worsen in the evenings and at night, and patients experience periodic limb movements during sleep. Although the syndrome is sometimes observed in patients with peripheral neuropathy, most of the time it is not accompanied by neuropathy.

There is an association between restless limbs and a deficiency of brain dopamine and iron deficiency.71 Therefore, checking iron and ferritin levels is part of the evaluation for this movement disorder.

If iron deficiency is detected, it should be evaluated (with an anemia workup) and treated with iron supplementation. If a sleep study reveals sleep apnea together with periodic limb movements during sleep, the apnea should be treated.

Symptomatic treatment of restless legs and limb movements during sleep usually begins with a dopamine agonist, such as pramipexole or ropinirole.72 Dopamine agonists have longer durations of action compared with levodopa, and one or two evening or bedtime doses may suffice.

If dopamine agonists are not well tolerated, a controlled-release formulation of carbidopa/levodopa should be tried next, and the dose should be titrated as tolerated. Other adjunct medications include gabapentin, benzodiazepines, and low-potency opiates as a last resort.

Wilson’s Disease

Wilson’s disease is a rare autosomal recessive disorder of copper metabolism that causes a buildup of the mineral in the liver, brain, eye, and other organs. It is a disease of children, adolescents, and young adults.53 The neurological manifestations include large-amplitude tremor, dystonia, chorea, and ataxia.74

Neurological manifestations may occur in the absence of hepatic disease. The diagnosis depends on a high index of suspicion, a low serum ceruloplasmin level, and high urinary excretion of copper.

Medical therapies include (1) reducing copper in the diet (foods such as shellfish, liver, mushrooms, some legumes, chocolate, soy, bran, and avocado), (2) supplementing with zinc, and (3) using chelating agents such as penicillamine or trientine. In cases of chronic hepatic failure, liver transplantation is an option.

Conclusion

Advances in the treatment of PD and other movement disorders continue to provide new strategies in symptomatic management of motor and nonmotor symptoms. Atypical neuroleptic agents have significantly reduced the incidence of tardive dyskinesia. Newer or rediscovered older drugs, as well as functional neurosurgery, have provided better relief of motor fluctuations in PD. However, definitive neuroprotection and effective restorative therapy for degenerative diseases remain elusive. Neuroimaging techniques need to be refined to enhance our ability to follow disease progression at the cellular level. Future drug therapy for PD is focusing as much on neuroprotection as on alleviating motor symptoms.
References


Continuing Education for Physicians and Pharmacists

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Expiration Date: April 30, 2006

TOPIC: Movement Disorders: Overview and Treatment Options

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Continuing Education Questions for Physicians and Pharmacists

TOPIC: Movement Disorders: Overview and Treatment Options

ACPE Program # 079-999-05-016-H01

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

Multiple Choice
Select the one correct answer.

1. Select the false statement concerning terminology related to movement disorders:
   a. Action tremor can be postural, intention, or task-specific.
   b. Signs seen in Parkinson's disease include tremor, rigidity, bradykinesia, and postural instability.
   c. Negative myoclonus is a sudden, brief muscle contraction, whereas positive myoclonus is an interruption of muscle contraction in the extended arm and wrist that causes inhibition of the activated muscle.
   d. Chorea resembles exaggerated fidgetiness.

2. Concerning movement disorders, select the false statements:
   a. “Writer's cramp” is a focal hand dystonia.
   b. The term choreoathetosis refers to slow and writhing movements.
   c. Impaired motor coordination, ballismus, is characterized by slurred speech, nystagmus, dysmetria, poor dexterity, and a wide-based gait.
   d. Dyskinesia in patients with Parkinson's disease results from the long-term complications of levodopa therapy.

3. The following statement is false for the treatment of essential tremor:
   a. The starting dose for primidone is 50 mg at bedtime, with doses gradually increasing up to 750 mg daily.
   b. Side effects associated with primidone include somnolence, fatigue, cognitive problems, and ataxia.
   c. Propranolol should be started at 50 mg daily and titrated as tolerated to 320 mg daily.
   d. Topiramate, gabapentin, benzodiazepines, and botulinum toxin may help relieve tremor.

4. Which of the following statements is true regarding neuroprotective agents for Parkinson's disease?
   a. There is no unequivocal agent available at this time.
   b. Coenzyme Q10 may slow symptom progression in early Parkinson's disease.
   c. Vitamin E was not beneficial in a large multicenter trial in patients with early Parkinson's disease.
   d. All of the above

5. Which of the following statements concerning dopamine agonists is false?
   a. Dopamine agonists cause less dyskinesia than levodopa.
   b. Dopamine agonists may be used as monotherapy for the first few years of Parkinson's disease.
   c. The side effects of dopamine agonists include nausea and hypotension.
   d. Dopamine agonists have more antiparkinson efficacy than levodopa does.

6. Which of the following statements is true concerning pharmaceutical treatments of nonmotor symptoms of Parkinson's disease?
   a. Memantine was found to be effective in treating dementia associated with Parkinson's disease in large studies.
   b. Risperidone is associated with fewer extrapyramidal adverse drug effects compared with quetiapine in patients with Parkinson's disease.
   c. Drowsiness and urinary urgency can be treated with peripheral anticholinergic agents.
   d. Levodopa is more likely than dopamine agonists to induce hallucinations.

7. Regarding dystonia, which statement is incorrect?
   a. Botulinum toxin injections are the first line of therapy for most focal dystonias.
   b. Focal dystonias may first be treated effectively with anticholinergic agents, benzodiazepines, or muscle relaxants at any dose with no insurmountable side effects.
   c. Botulinum toxin is not appropriate for the treatment of generalized dystonia.
   d. Anticholinergic agents, benzodiazepines, muscle relaxants, and anticonvulsants are frequently used to treat generalized dystonia.

8. Which of the following statements is incorrect?
   a. In patients with cortical myoclonus, the most commonly used drugs are valproic acid, clonazepam, and primidone.
   b. Benzodiazepines may help to suppress chorea in a variety of disorders.
   c. Anticholinergic medications are very effective in alleviating tardive dyskinesia; however, it may cause agranulocytosis, and blood count monitoring is necessary.
   d. Clozapine has the most proven efficacy among neuroleptic agents in alleviating tardive dyskinesia; however, it may cause agranulocytosis, and blood count monitoring is necessary.

9. Which of the following classes of drugs are used to treat tic disorders?
   a. Alpha-adrenergic agonists
   b. Neuroleptic agents
   c. Benzodiazepines
   d. All of the above

10. Regarding restless limbs syndrome, which statement is incorrect?
   a. There is an association between restless limbs and a deficiency of brain dopamine and iron.
   b. Symptomatic treatment of the syndrome begins with dopamine agonists.
   c. First-line medications include gabapentin and benzodiazepines.
   d. If dopamine agonists are not well tolerated, a controlled-release formulation of carbidopa/levodopa should be tried next.
CE Registration and Evaluation Form

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Title: Movement Disorders: Overview and Treatment Options
Authors: Ali Samii, MD, and Bruce R. Ransom, MD, PhD
Submission deadline: April 30, 2006
ACPE Program # 079-999-05-016-H01

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Please fill in the box next to the letter corresponding to the correct answer
1. a □ b □ c □ d □ 6. a □ b □ c □ d □
2. a □ b □ c □ d □ 7. a □ b □ c □ d □
3. a □ b □ c □ d □ 8. a □ b □ c □ d □
4. a □ b □ c □ d □ 9. a □ b □ c □ d □
5. a □ b □ c □ d □ 10. a □ b □ c □ d □

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Rate the extent to which: Very High High Moderate Low Very Low
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2. You were satisfied with the overall quality of this activity
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