

How best to address these common movement disorders

This review describes how to manage everything from Parkinson's disease and tic disorders to restless legs syndrome and ataxia.

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PRACTICE RECOMMENDATIONS

➤ *Initiate neuroprotective therapy with a monoamine oxidase B inhibitor to slow the progression of Parkinson's disease. With onset of functional impairment, give levodopa at the lowest effective dose. (A)*

➤ *Give propranolol for essential tremor causing a patient distress, starting at 20 to 40 mg twice daily and increasing the dose (to a maximum of 320 mg/d) until relief is achieved. (B)*

➤ *Consider giving a dopamine receptor blocker for Tourette syndrome or other tic disorder; alternative agents are clonidine or a newer agent, tetrabenazine. (B)*

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Movement disorders often require consultation with a neurologist, and a working knowledge of established and novel treatments can set the stage for optimal long-term cooperative management.¹ In this article, we review therapeutic options for common movement disorders, including hypokinetic, hyperkinetic, and dyskinetic disturbances.

Parkinson's disease treatment: MAO-B inhibitor, levodopa are mainstays

Parkinson's disease, the most common hypokinetic movement disorder, is a chronic, progressive, neurodegenerative disease. It affects 1% of individuals older than 65 years and 4% to 5% of individuals older than 85 years. Its cardinal symptoms are resting tremor, bradykinesia, rigidity, a flexed posture, and loss of postural reflexes. Resting tremor, referred to as "pill rolling" tremor, is 4 to 6 Hz and usually begins unilaterally.^{2,3} Associated symptoms can include dystonia, dementia, psychiatric disorders, sleep disorders, and autonomic symptoms.

■ **Neuroprotective therapy** is used to slow the progression of the disease, particularly in its early stage. The monoamine oxidase B (MAO-B) inhibitor selegiline has proven effective in this regard² (strength of recommendation [SOR]: A). In randomized controlled studies, selegiline has delayed the need for levodopa for 9 to 12 months⁴ (SOR: A). Another MAO-B inhibitor, rasagiline, has demonstrated neuroprotective effects as well⁵ (SOR: B). These medications may also be used with levodopa for symptom control and as adjunct therapy in patients with motor fluctuations.² A conventional dose of selegiline is 10 mg/d (5 mg at breakfast; 5 mg at lunch). Rasagiline is given at 1 mg/d. Concomitant use of ciprofloxacin or other CYP1A2 inhibitors limits its effectiveness.^{6,7}

■ **Symptomatic therapy** is indicated at the onset of functional impairment. The dopamine precursor levodopa is the most widely used and effective drug for Parkinson's disease

➤ **Propranolol is more effective for hand and forearm tremor than for head and voice tremor.**

symptoms, especially bradykinesia and rigidity. Use the lowest possible dose to control symptoms (eg, 100 mg twice daily) and protect against motor complications of the drug⁷⁻⁹ (SOR: A). To prevent conversion of levodopa to dopamine outside the blood-brain barrier, combine it with the decarboxylase inhibitor carbidopa. Dietary restriction of proteins may be needed, because amino acids can interfere with the absorption of levodopa.

Especially with prolonged use, levodopa can cause disturbing adverse effects, such as nausea, vomiting, psychosis, cardiac arrhythmia, and orthostatic hypotension. Dyskinesias and motor fluctuations are complications of long-term treatment and are irreversible. Adding a catechol-O-methyltransferase (COMT) inhibitor, such as entacapone, to increase levodopa's effectiveness has been shown to reduce motor fluctuations^{2,3,10} (SOR: B). Dopamine agonists such as bromocriptine, ropinirole, and pramipexole used in early Parkinson's disease can also reduce dyskinesias and motor fluctuations. Dopamine agonists may be preferred to levodopa in early Parkinson's disease because they are better tolerated and cause fewer adverse effects. Or they may be used as adjuncts for patients whose response to levodopa is deteriorating or fluctuating^{3,7,8} (SOR: B). In advanced disease, motor complications can also be managed by augmenting levodopa therapy with a dopamine agonist, MAO-B inhibitor, or COMT inhibitor^{7,8} (SOR: A).

Anticholinergics, mainly benztropine and trihexyphenidyl, may be used as symptomatic treatment, especially in young people with early Parkinson's disease and severe tremor. However, they are not the first drugs of choice due to limited efficacy and the potential for neuropsychiatric side effects⁸ (SOR: C). Amantadine can reduce dyskinesia in people with advanced Parkinson's disease⁸ (SOR: C). For patients who have Parkinson's disease with severe motor complications, intermittent apomorphine injections can help reduce "off time" periods in the daily treatment cycle when the efficacy of drugs wanes⁹ (SOR: B).

Deep brain stimulation of the subthalamic nucleus has only SOR C support for reducing dyskinesias and off time.⁹

Treating nonmotor symptoms of Parkinson's disease can be challenging. For dementia in these patients, consider cholinesterase inhibitors^{6,8} (SOR: C). For depression, selective serotonin reuptake inhibitors are effective^{6,8,9} (SOR: C). For psychosis, preferred agents are low-dose clozapine or quetiapine^{6,8-10} (SOR: C). Plan for supportive and symptomatic management of constipation, dysphagia, sialorrhea, orthostatic hypotension, sleep disturbances, and urinary urgency.^{2,3}

Tremor

Tremor is a common form of hyperkinesia, presenting either as a primary disorder or as a symptom of another condition.¹¹ By definition, it is a rhythmical, involuntary, oscillatory movement of 1 or more body parts. Tremors are classified as rest or action tremors, with the latter being further categorized as postural (occurring while the patient maintains a position against gravity) or kinetic (occurring during voluntary movement).^{2,10}

Physiologic tremor: Pharmacologic Tx is usually not needed

Physiologic tremor is benign, high frequency (8-12 Hz), low amplitude, and postural. An exaggerated form of this tremor may result from anxiety, hyperthyroidism, pheochromocytoma, hypoglycemia, excessive caffeine consumption, fever, withdrawal from opioids and sedatives, and some medications. No drug treatment is necessary unless symptoms become bothersome. Correct the underlying cause or have the patient avoid the triggering factor, and offer reassurance that the condition is not pathological or progressive.^{2,12} For anxiety, consider cognitive-behavioral/relaxation therapy or benzodiazepines (if tremor did not result from withdrawal of benzodiazepines) or beta-adrenergic antagonists (eg, propranolol).^{12,13}

Essential tremor: Try propranolol or primidone first

Essential tremor (ET) is the most common movement disorder. It often results in functional disability and leads to many physical and emotional difficulties. ET is bilateral, usually symmetric (although mild asymmetry is possible), and postural or kinetic, typically

affecting hands and forearms. The frequency of ET is 4 to 12 Hz. Cranial musculature may be involved in 30% of cases, affecting the head and voice.³ Prevalence ranges from 4 to 40 cases per 1000 people. The age-adjusted incidence is 17.5/100,000 per year; it peaks during the teen years and the fifth decade.^{2,3}

Autosomal dominant type of inheritance is common, and a family history of ET is often present, particularly with younger patients. The differential diagnosis includes Parkinson's disease tremor; dystonic, cerebellar, rubral, and psychogenic tremors; and asterixis.³ Unlike ET, many of these disorders have associated neurologic, psychiatric, or systemic signs.

Treatment with propranolol or primidone is indicated if ET causes functional impairment or social or emotional problems for the patient.^{2,3,10,13} Both propranolol and primidone reduce limb tremor^{2,10,13} (SOR: B), but only propranolol is approved by the US Food and Drug Administration (FDA) for treatment of ET. Propranolol is more effective for hand and forearm tremor than for head and voice tremor. Start propranolol at 20 to 40 mg twice a day and increase the dose as needed to achieve symptom relief.¹⁴

A maintenance dose of 240 to 320 mg/d may be needed. Major adverse effects are fatigue, sedation, depression, and erectile dysfunction. Contraindications to propranolol include asthma, second-degree atrioventricular block, and insulin-dependent diabetes.

If starting with primidone alone, prescribe at a dose <25 mg at bedtime and increase the dose slowly over several weeks to prevent onset of nausea, vomiting, sedation, confusion, or ataxia. The maximum allowable dose is 750 mg/d in 3 divided doses.¹⁰ Primidone and propranolol may be used in combination to treat limb tremor when monotherapy is insufficient (SOR: B).¹³

Thirty percent of patients with ET will not respond to propranolol or primidone. An alternative choice is the anticonvulsant gabapentin^{10,12-14} (SOR: C). However, clinical experience with it is limited. Lethargy, fatigue, decreased libido, dizziness, nervousness, and shortness of breath are adverse effects of gabapentin; they are usually mild and tolerable.¹³ Topiramate is another option that seems to be as effective as gabapentin^{10,13} (SOR: C), but studies of long-

term outcomes are lacking. Topiramate's side effects include weight loss and paresthesias. Additionally, alprazolam, clonazepam, clozapine, olanzapine, atenolol, sotalol, nadolol, and nimodipine may reduce limb tremor² (SOR: C). Alcohol reduces tremor amplitude in 50% to 90% of patients, but tremor may worsen after the effect of alcohol has worn off.¹⁵

For patients with essential hand tremor that fails to respond to oral agents, consider botulinum toxin A¹⁶ (SOR: B). However, it is also associated with dose-dependent hand weakness¹⁶ (SOR: C). Botulinum toxin may reduce head and voice tremor¹⁶ (SOR: C), but hoarseness and swallowing difficulties may occur after use for voice tremor.¹⁶

Invasive therapies may benefit patients with refractory tremor. Deep brain stimulation and thalamotomy are highly effective in reducing limb tremor¹³ (SOR: C). Each carries a small risk of major complications. Some deep brain stimulation adverse events may resolve with time. Other adverse events may resolve with adjustment of stimulator settings. No evidence exists for surgical treatment for voice and head tremor or for gamma-knife thalamotomy.¹³

Drug-induced tremor

Drugs with the potential to cause postural tremor, intention tremor, or rest tremor include the following:¹⁵

- alcohol (chronic)
- amiodarone
- amphetamines
- beta-adrenergic agonists
- caffeine
- calcitonin
- carbamazepine
- cocaine
- cyclosporine
- dopamine
- lithium
- metoclopramide
- neuroleptics
- procainamide
- steroids
- theophylline
- thyroid hormones
- tricyclic antidepressants
- trifluoperazine
- valproic acid



Tic disorders, including Tourette syndrome, rarely require drugs.

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With drug-induced tremor, carefully evaluate a patient's need for the drug. Discontinue the offending agent if possible, or try lowering the dose.

**Psychogenic tremor:
 A history of somatization is a clue**

Psychogenic tremor can occur at rest or during postural or kinetic movement. Clinical features include an abrupt onset, a static course, spontaneous remission, and unclassifiable tremors.¹⁷ Psychogenic tremor increases under direct observation and decreases with distraction. Patients with psychogenic tremor often have a history of somatization.¹⁸ Electrophysiologic testing can help confirm the diagnosis. If remission does not occur spontaneously, patients may find relief with psychotherapy or placebo.¹⁹

**Tic disorders:
 Opt for dopamine receptor blockers**

Tics are involuntary or semivoluntary movements or sounds that are sudden, brief, intermittent, repetitive, nonrhythmic, unpredictable, and purposeless. Tics can occur in any part of the body.²⁰

The most common tic disorder is Tourette syndrome—a combination of motor and phonic tics with onset before age 21. It affects approximately 5 to 10 children out of 10,000. Boys are more commonly affected than girls. Attention deficit hyperactivity disorder frequently accompanies this syndrome.²

The goal of treatment with any tic disorder is to improve social functioning, self-esteem, and quality of life. Education and support of patients is important. Tic disorders, including Tourette, rarely require drugs. But if tics become too distressing, first-line treatment would be a dopamine modulator, tetrabenazine, or clonidine. Randomized controlled trials with various neuroleptics have revealed dramatic reductions in tic severity. However, many patients do not tolerate the acute adverse effects (most commonly sedation, weight gain, depression, lethargy, and akathisia), and prolonged treatment confers a small risk of tardive dyskinesia. Behavioral therapy is an important part of management.²⁰

Dopamine-receptor blocking drugs such

as haloperidol, pimozide, and fluphenazine are the most effective treatment for tics²⁰ (SOR: B). Tetrabenazine is a promising new dopamine-depleting drug; controlled trials are ongoing^{2,20} (SOR: B). Clonidine, an alpha 2-adrenergic agonist, is useful in treating patients with Tourette syndrome, helping to improve sleep and attention^{2,21} (SOR: C). Medically refractory motor and disabling phonic tics such as coprolalia can be ameliorated by botulinum toxin injections²¹ (SOR: B). Deep brain stimulation is being used at an increasing rate for medically refractory tics in Tourette syndrome²¹ (SOR: B).

**Restless legs syndrome:
 Dopamine agonists are preferred**

Restless legs syndrome (RLS) is a disorder characterized by sensory symptoms and motor disturbances of the legs, mainly during rest. Treatment may not be necessary for patients with mild or sporadic symptoms. For moderate to severe RLS with significant impairment, dopamine agonists are the preferred agents²² (SOR: A). RLS can also occur secondary to such conditions as iron deficiency and uremia, and correction of the underlying disorder is the goal. Prescribe iron replacement for patients with a ferritin level <50 ng/mL²² (SOR: C). Medications known to cause or exacerbate the symptoms of RLS are antidopaminergic agents (such as neuroleptics), diphenhydramine, tricyclic antidepressants, alcohol, caffeine, lithium, and beta-blockers. If a patient is taking medications that exacerbate symptoms of RLS, discontinue them and use appropriate substitutes²² (SOR: C).

**Myoclonus:
 Clonazepam for essential disorder**

Myoclonus is a brief, sudden, shock-like movement caused by involuntary muscle contractions or lapse of muscle contraction (asterixis). Given the complex origins of myoclonus, multiple drugs may be needed. Essential myoclonus is disabling and can be treated with clonazepam. Start with 0.25 mg orally twice daily, and increase the dosage over 3 days to 1 mg/d²³ (SOR: C). Most cases of myoclonus are secondary due to drugs such as lithium,

➤ Restless legs syndrome can occur secondary to iron deficiency and uremia; correction of the underlying disorder is key.

toxins, advanced liver disease, infections including human immunodeficiency virus, dementia, and brain lesions. Treatment should also address the underlying disorder.^{2,23}

Chorea

Chorea is an abnormal involuntary movement disorder described as “a state of excessive, spontaneous movements, irregularly timed, nonrepetitive, randomly distributed, and abrupt in character.”²⁴

Treatment of chorea is symptomatic, aiming to reduce morbidity and prevent complications. Haloperidol and fluphenazine are effective but can impair voluntary movements^{2,10,25} (SOR: C). The dopamine-depleting drugs reserpine and tetrabenazine are also effective^{2,10,25} (SOR: C). GABAergic drugs, such as clonazepam, gabapentin, and valproate, can be used adjunctively.^{10,25}

Dystonia

Dystonia is a syndrome involving sustained contractions of opposing muscles that cause twisting, repetitive movements and abnormal

postures. Primary dystonia can be treated successfully with high doses of trihexypenidyl alone, starting with 1 mg orally per day and increasing gradually to 6 to 80 mg/d until symptoms are controlled; or in combination with baclofen, starting with 10 mg orally once daily and increasing to a maximum dose of 30 to 120 mg/d^{1,2} (SOR: C).

Consider botulinum neurotoxin injection for focal upper extremity dystonia and adductor spasmodic dysphonia¹⁶ (SOR: B).

Ataxia

Ataxia is an unsteady gait associated with cerebellar dysfunction, proprioceptive defects, or both. Ataxia may be primary (Friedreich ataxia and spinocerebellar ataxia) or secondary to stroke, trauma, alcoholic degeneration, multiple sclerosis, vitamin B12 deficiency, and hydrocephalus. Treatment, when possible, should target the underlying cause.^{1,2}

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➤ Consider botulinum neurotoxin injection for focal upper extremity dystonia and adductor spasmodic dysphonia.

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