MOVEMENT DISORDERS: THERAPY UPDATE FOR THE MODERN CLINICIAN

PROCEEDINGS OF A SYMPOSIUM

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Description
Modern clinicians recognize that therapeutic advances for movement disorders are occurring at an unprecedented pace. This continuing medical education (CME) activity addresses clinicians’ need for up-to-date therapeutic information that enhances their ability to provide comprehensive care in a manner that is both efficient and compassionate.

Objectives
Upon completing this activity, participants will be able to:
• Review the current treatment options for the newly diagnosed Parkinson disease (PD) patient
• Discuss the promising and future therapies for PD
• Recognize and treat the most common nonmotor problems associated with PD
• Select patients who are candidates for deep brain stimulation (DBS)
• Discuss why DBS failures occur and know how to manage them
• Classify and provide a treatment plan for the dystonic patient
• Describe when and how to use botulinum toxin therapy
• Review the latest treatments for tics, choroas, and other movement disorders.

Target Audience
This activity is intended for neurologists, internists, family physicians, and interested allied health professionals.

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Introduction

The pharmacologic options for movement disorders are increasing, with more than 12 drugs available in the United States for treatment of Parkinson disease (PD) and many more under investigation. In addition, some patients with movement disorders may be candidates for surgical therapies. Still, challenges remain. Early PD requires skillful decision-making to maximize the potential benefits of levodopa, for example. Expertise is necessary to select appropriate candidates for deep brain stimulation and other surgical options. Developing a management plan for patients who have Huntington disease requires considerable proficiency.

This Cleveland Clinic Journal of Medicine supplement addresses these and other challenges faced by clinicians who care for patients with movement disorders. The supplement, a continuing medical education activity, presents the proceedings of a symposium, “The Annual Therapy Symposium on Movement Disorders for the Modern Clinician,” held in Fort Lauderdale, Florida, on January 29, 2011. Clinicians who read the proceedings will find guidance for selection of pharmacologic therapy, a detailed explanation of deep brain stimulation, practical recommendations for managing motor and nonmotor complications of PD, and other useful information that will enhance the care of patients with movement disorders.

Hubert H. Fernandez, MD
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Managing the patient with newly diagnosed Parkinson disease

**ABSTRACT**

The treatment of early Parkinson disease (PD) is generally symptomatic, although therapy that also offers neuroprotection in early-stage PD would be welcomed. Levodopa remains the most effective agent for relief of PD symptoms, but chronic levodopa therapy is associated with motor fluctuations and dyskinesias, and clinicians may therefore opt to postpone its use. Alternatives to levodopa in early PD include monoamine oxidase (MAO)-B inhibitors, amantadine, and dopamine agonists. MAO-B inhibitors have only mild symptomatic effects. Amantadine is associated with improvement in functional disability and, in a subset of PD patients, a robust symptomatic improvement. Dopamine agonists improve symptoms and may have a neuroprotective effect. Partial dopamine agonists, adenosine A<sub>2A</sub>-receptor antagonists, and safinamide are symptomatic therapies that are under investigation. Neuroprotective strategies under study include enhancement of mitochondrial function, antiinflammatory mechanisms, calcium channel blockade, and uric acid elevation. Deep brain stimulation may slow cognitive and motor decline when used in early PD. Stem cell therapy and gene therapy are still under investigation.

Parkinson disease (PD) is a slowly progressive neurodegenerative disorder. Early PD, or stage 1 or 2 on the Unified Parkinson’s Disease Rating Scale (UPDRS), is characterized by mild symptoms, minimal to mild disability, and lack of postural instability or cognitive decline. The goal of therapy in PD is to help patients retain functional independence for as long as possible. Therapeutic choices in early PD are guided by the effect of symptoms on function and quality of life, consideration of complications associated with long-term levodopa, the likelihood of response fluctuations to levodopa, and the potential for a neuroprotective effect.

**SYMPTOMATIC THERAPIES IN EARLY PD**

Dopaminergic replacement therapy with levodopa is a legitimate choice for the treatment of early PD. Use of carbidopa-levodopa has been shown to slow the progression of PD in a dose-dependent manner as evidenced by a decrease in total score on the UPDRS in patients with early PD who were randomly assigned to receive carbidopa-levodopa compared with those who received a placebo.1

Alternatives to levodopa

There are several reasons to choose an alternative to levodopa for the treatment of early PD. The first is to postpone the development of levodopa-induced dyskinesias, which are linked to duration of levodopa treatment and total exposure to levodopa. The second is postponement of the “wearing-off” effect; that is, the reemergence of symptoms that occurs in some patients before their next scheduled dose of levodopa. Such reasoning applies to early PD patients with minimal or no disability and—in particular—to young-onset PD patients who tend to develop vigorous dyskinesias and dramatic wearing-off phenomena. Pharmacologic alternatives to levodopa in early PD include monoamine oxidase (MAO)-B inhibitors, amantadine, and dopamine agonists.

**MAO-B inhibitors.** Two MAO-B inhibitors are approved by the US Food and Drug Administration for the treatment of PD: rasagiline and selegiline. These agents have a mildly symptomatic effect. In the Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) trial, use of rasagiline at doses of 1 and 2 mg/d slowed the rate of worsening of the UPDRS score compared with placebo in patients with untreated PD (Figure 1).2 Patients were randomly assigned to an early-start group (rasagiline, 1 or 2 mg/d, or placebo for 72 weeks) or a late-start group (placebo for 36 weeks followed by rasagiline, 1 or 2 mg/d, or placebo for 36 weeks). The rate of change in the UPDRS score was...
Early Parkinson Disease

Rasagiline at doses of 1 mg/day (A) and 2 mg/day (B) slowed the rate of worsening of the Unified Parkinson’s Disease Rating Scale (UPDRS) score compared with placebo in patients with untreated Parkinson disease.2


Amantadine. In an early study of 54 patients with PD, functional disability scores improved significantly with administration of amantadine 200 to 300 mg/d compared with placebo.3 A small subset of patients, perhaps 20% or less, who are treated with amantadine experience robust symptom improvement. Side effects of amantadine include hallucinations, edema, livedo reticularis, and anticholinergic effects. A more recently discovered potential side effect is corneal edema.

Dopamine agonists. Pramipexole (immediate-release [IR] and extended-release [ER]), and ropinirole IR and ER are dopamine agonists that have demonstrated disease-modifying effects and efficacy in improving PD symptoms.

Pramipexole ER administered once daily in early PD was shown to be superior to placebo on the mean UPDRS total score.5 Ropinirole ER produced mean plasma concentrations over 24 hours similar to those achieved with ropinirole IR, and showed noninferiority to ropinirole IR on efficacy measures in patients with de novo PD.5

The effective dosage range of pramipexole ER in early PD is 0.375 to 4.5 mg/d. Side effects include hallucinations, edema, excessive diurnal somnolence, and impulse control disorders (ie, pathologic gambling, hypersexuality, excessive craving for sweets). Compared with pramipexole IR, compliance is enhanced with the ER formulation because of ease of administration, but this formulation also is more expensive.

In early PD, the effective dosage range of ropinirole ER is 8 to 12 mg/d.6 The side effects are the same as with pramipexole ER with the same compliance advantage and cost disadvantage compared with the IR formulation.

Research indicates that dopamine agonists may have a neuroprotective effect. In two large clinical trials in which patients with PD were followed with an imaging marker of dopamine neuronal degeneration (using single-photon emission computed tomography or positron emission tomography), recipients of pramipexole7 or ropinirole8 showed slower neuronal deterioration compared with levodopa recipients. A counterargument to the neuroprotective theory is that these differences between the dopamine agonists and levodopa reflect neurotoxicity of levodopa rather than neuroprotection by dopamine agonists. The absence of a placebo comparison in both trials adds to the difficulty

slowed significantly with early treatment with rasagiline at a dosage of 1 mg/d, but not at 2 mg/d. Because the hierarchical primary end points for the ADAGIO trial were met only for the cohort receiving 1 mg of rasagiline early, it remains inconclusive whether rasagiline has a neuroprotective effect.

In a placebo-controlled study of selegiline in de novo early-phase PD, Pålhagen et al showed that selegiline monotherapy delayed the need for levodopa. When used in combination with levodopa, selegiline was able to slow the progression of PD as measured by the change in UPDRS total score.3

In a placebo-controlled study of selegiline in de novo early-phase PD, Pålhagen et al showed that selegiline monotherapy delayed the need for levodopa. When used in combination with levodopa, selegiline was able to slow the progression of PD as measured by the change in UPDRS total score.3
Symptomatic Therapies: The Future

Nonergoline dopamine agonist. Transdermal rotigotine is a nonergot D₁/D₂/D₃ agonist. Higher doses produce higher plasma levels of rotigotine, which remain steady over the 24-hour dosing interval. Transdermal rotigotine has demonstrated effectiveness in early PD in several clinical trials. The patch, applied once daily, provides a constant release of medication. Removing the patch immediately interrupts drug administration.

Rotigotine patches must be refrigerated to prevent crystallization, a requirement that has delayed the product’s arrival on the market. The patch is reputed to be difficult to peel from its backing and apply. Skin reactions are a side effect, and nonergot side effects are possible. Despite these drawbacks, transdermal rotigotine represents a convenient option for perioperative management of PD and in patients with dysphagia.

Exercise. Exercise has symptomatic and possibly neuroprotective benefits in PD, supporting its use as an additional medical measure. Evidence supports the value of treadmill walking and high-impact exercise in improving stride length, quality of life, and motor response to levodopa.

Symptomatic Therapies: The Future

Partial dopamine agonists

Pardoprunox is a partial dopamine agonist with full 5-HT₁A-agonist activity. A partial dopamine agonist acts in two ways: (1) It stimulates dopamine production in brain regions with low dopamine tone, and (2) it has dopamine antagonist activity under circumstances of high dopamine sensitivity, theoretically avoiding overstimulation of dopamine receptors. Because it inhibits excessive dopamine effect, pardoprunox may prevent dyskinesia. In addition, because pardoprunox has serotonin agonist activity, it may also act as an antidepressant.

Partial dopamine agonists

In a phase 2 study, significantly more patients randomized to pardoprunox had a 30% or greater reduction in UPDRS motor score compared with placebo at end-of-dose titration (35.8% for pardoprunox vs 15.7% for placebo; P = .0065) and at end point (50.7% for pardoprunox vs 15.7% for placebo; P < .0001).

Adenosine A₂A-receptor antagonists

Adenosine A₂A receptors are located in the basal ganglia, primarily on gamma aminobutyric acid (GABA)-mediated enkephalin-expressing medium spiny neurons in the striatum. These receptors modulate dopamine transmission by opposing D₂-receptor activity. The D₂ pathway is an indirect pathway that promotes suppression of unnecessary movement.

Two A₂A-receptor antagonists have demonstrated efficacy in clinical trials. Vipadenant has been proven effective as monotherapy in phase 2 clinical trials. Vipadenant has been shown to improve “off time” as an adjunct to levodopa without increasing dyskinesia.

Safinamide

Safinamide, currently in phase 3 clinical trials, has three mechanisms of action. It is an inhibitor of dopamine reuptake, a reversible inhibitor of MAO-B, and an inhibitor of excessive glutamate release. The addition of safinamide to a stable dose of a single dopamine agonist in patients with early PD resulted in improvement of motor symptoms and cognitive function.

Neuroprotective Strategies under Investigation

Four neuroprotective strategies are under study: enhanced mitochondrial function, antiinflammatory mechanisms, calcium channel blockade, and uric acid elevation.

Enhanced mitochondrial function

Creatine has generated interest as a disease-modifying agent in response to preclinical data showing that it could enhance mitochondrial function and prevent mitochondrial loss in the brain in models of PD. Creatine is now the subject of a large phase 3 National Institutes of Health–sponsored clinical trial in patients with early-stage PD.

Coenzyme Q10 (CoQ 10) exhibited a trend for neuroprotection at 1,200 mg/d, lowering the total mean UPDRS score compared with placebo in a 16-month study. Current efforts are directed at determining whether 1,200 or 2,400 mg/d of CoQ10 are neuroprotective. A nanoparticle form of CoQ10, 100 mg three times a day, has been shown to produce plasma levels of CoQ10 equivalent to those produced by 1,200-mg doses of the standard form. CoQ10 is free of symptomatic effects.

Antiinflammatory mechanisms

Parkinson disease may have an important inflammatory component. A meta-analysis of seven studies showed an overall hazard ratio of 0.85 for development of PD in users of nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs), with each of the seven studies demonstrating a hazard ratio less than 1. A similar meta-analysis showed no such association. Further study is warranted.

Calcium channel blockade

A sustained-release formulation of isradipine, an L-type calcium channel blocker, is being studied in a phase 2
Uric acid elevation
Urate concentration in the cerebrospinal fluid predicts progression of both cognitive and motor decline when STN DBS was administered earlier in the course of Parkinson disease (PD). Late STN DBS is favored if the annual rate of motor progression is greater than 25%, but this is an unrealistic scenario for PD.21

Stem cell therapy
Stem cells obtained from blastocytes, fibroblasts, bone marrow, or the adult, embryonic, or fetal central nervous system through “molecular alchemy” can form dopaminergic neurons. Given the high cost and potential risks of stem cell therapy, it must be proven superior to DBS to be considered an option for early PD. Several practical problems act as hurdles to successful stem cell therapy. Efficient generation of dopamine-producing neurons and successful grafting are required. Tumor growth is a risk. Involuntary movements have been observed in some patients who received fetal implants. A limitation of stem cell therapy is that it will only affect those aspects of PD that are dependent on dopamine.

Gene therapy
Gene delivery of the growth factor analogue adeno-associated type-2 vector (AAV2)-neurturin has been investigated in patients with advanced PD. When surgically placed inside a neuron, neurturin enhances neuron vitality, enabling it to better fight oxidative stress and other attacks. It fared no better than sham surgery on changes in UPDRS motor score at 12 months in a randomized trial.22 A few patients enrolled in this trial have been followed for longer than 12 months, at which time the mean change in motor scores appears to favor the group assigned to gene delivery of AAV2-neurturin. A phase 1/2 trial is investigating the safety and efficacy of bilateral intraputaminal and intranigral administration of neurturin.

SUMMARY
Levodopa is a legitimate choice for the treatment of early PD; experimental evidence in animals suggests that it may be neuroprotective against PD.

Uric acid elevation
Urate concentration in the cerebrospinal fluid predicts progression of PD, with higher levels associated with slower progression of disease.20 Urate may delay oxidative destruction of dopaminergic neurons that occurs with progression of PD. Pharmacologic elevation of uric acid is being explored as a treatment option in PD.
Early DBS is a new avenue of investigation as a potential disease modifier. Stem cells are still being studied and limitations of sufficient production and potential tumor growth, among others, have delayed the institution of clinical trials. Gene therapy is an interesting additional treatment modality in active research.

REFERENCES


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Off spells and dyskinesias: Pharmacologic management of motor complications

ABSTRACT

There are two major causes of disability in patients with Parkinson disease: motor fluctuations that occur when a dose of levodopa becomes ineffective, leading to a “wearing off,” and hyperkinetic movements (dyskinesias) caused by excessive levels of dopamine. The utility of continuous levodopa treatment is therefore limited by motor complications. Pharmacologic options to treat wearing off include adding (or increasing the dosage of) levodopa, adding (or increasing the dosage of) a dopamine agonist, or adjunctive treatment with a monoamine oxidase inhibitor or catechol-O-methyltransferase inhibitor. Dyskinesias will respond to a reduction in levodopa dosage at the expense of worsening parkinsonism and an increase in the number of “off” episodes. Continuous dopamine stimulation may overcome the pulsatile stimulation of postsynaptic dopamine receptors produced by standard oral formulations of levodopa that lead to motor complications.

Dopaminergic treatment is extremely beneficial in inducing symptom improvement in early Parkinson disease (PD). Patients typically experience a smooth and even response to the early stages of levodopa treatment. With disease progression, however, the effect of levodopa begins to weaken approximately 4 hours after each dose, leaving patients anticipating the need for their next dose and vulnerable to motor fluctuations and dyskinesias. Motor fluctuations refer to the unanticipated loss of effect of a given dose of levodopa; instead of a smooth, predictable symptomatic benefit, the patient may lose benefit earlier than usual (termed “wearing off”) or may suddenly switch from “on” (symptoms controlled) to “off” (symptoms return). Dyskinesias, or involuntary movements, occur when dopamine levels are too high.

Motor complications are a major cause of disability in PD. They affect 60% to 90% of PD patients after 5 to 10 years of treatment. Moreover, in one study of 143 PD patients, motor complications diminished quality of life; the most strongly affected dimensions were mobility, activities of daily living, communication, and stigma.

PATHOGENESIS OF MOTOR COMPICLATIONS

Under physiologic conditions, dopamine stimulation of the striatal dopamine receptors occurs in a sustained fashion. In early PD, the pool of remaining neurons of the substantia nigra is believed to be sufficiently active to smooth out changes in levodopa levels, providing a relatively constant amount of dopamine. Many PD patients therefore have several years of trouble-free treatment following diagnosis. In the advanced disease states, however, the number of presynaptic dopaminergic neurons progressively decreases. With fewer dopaminergic neurons, a constant dopaminergic concentration cannot be sustained. As PD advances, the progressive loss of dopaminergic neurons leads to impaired dopamine storage. Thus, the buffering capacity of dopaminergic neurons decreases and synaptic dopamine levels begin to reflect systemic or exogenous levodopa levels.

With disease progression, the “honeymoon” phase diminishes, and most PD patients begin to develop motor complications after 5 or more years. At this stage, medications frequently need to be adjusted, which can be a complex task for the physician and patient. The schema for the pathogenesis of motor complications related to the disease process and chronic levodopa treatment are depicted in the Figure.

According to current views, the total motor response to levodopa results from the combination of endogenous dopamine production along with the short-duration response (SDR) and the long-duration response (LDR) to exogenous levodopa. The SDR represents an improvement in parkinsonian symptoms and signs, lasting minutes to hours, that is closely related to the rise and fall of plasma levodopa concentrations. The SDR parallels the fluctuations in motor response and has received...
the most attention in the literature. The LDR is an improvement in parkinsonism that builds up over days and likewise decays over days. The LDR decays more rapidly in severely affected patients. Negative response, or “super off,” is a transient worsening of motor function to below the baseline level that may occur as the effects of the SDR dissipate.

The proportions of the SDR and LDR can vary according to disease progression. The LDR is more prominent in early stages, accounting for the stable response seen in the honeymoon period of treatment.

Peripheral factors
Additional peripheral factors such as changes in gastric motility and absorption contribute to motor complications. Levodopa is transported by a saturable active transporter system, the large neutral amino acid system, in the gut, and across the blood-brain barrier. Levodopa absorption is thus affected by food intake, especially protein. Levodopa and dietary amino acids compete with each other for absorption at the intestinal and blood-brain levels. Levodopa and other dopaminergic therapies further chronically reduce gastric emptying.

Pulsatile dopamine stimulation
The latency from the time of levodopa administration to the onset of motor improvement is typically 30 to 90 minutes. Latency is longer in late stages when the striatal buffer is weakened and the plasma concentration of levodopa fluctuates.

Types of motor fluctuations
Fluctuating motor response in levodopa-treated patients refers to clinically apparent oscillations in motor function. Management of the fluctuating response may require frequent daily dosing of levodopa.

Motor fluctuations in PD take four forms: wearing off, off, delayed on/no on, and dyskinesias.

Wearing off
Wearing off refers to the premature loss of benefit from a given dose of levodopa, causing a predictable return of parkinsonian symptoms (bradykinesia, tremors, rigidity, and gait problems) in advance of the next scheduled dose. Observed in early and moderate PD, wearing off is the most common type of motor fluctuation. Its pathophysiology relates to disease progression and pharmacokinetics of levodopa. It can be sudden or gradual, predictable or unpredictable.

Off state
The off state is the unpredictable reappearance of parkinsonian symptoms at a time when central levels of antiparkinsonian drugs are expected to be within the target therapeutic range. Such symptoms include pain, stiffness, paresthesia, cognitive symptoms (depression, anxiety, difficulty with concentration, and mental slowing), inner restlessness, and inner tremulousness. The off state can be sudden or gradual, predictable or unpredictable.

Delayed on/no on
Delayed on is a prolongation of the time required for the central antiparkinsonian drug effect to appear. As the disease progresses, wearing off becomes more complicated and more unpredictable. The dosing responses vary, and patients sometimes report delayed on. The causes of delayed on or no on can be an insufficient dose, dosing with high-protein meals, or delayed gastric emptying. Metoclopramide or domperidone can help with gastric emptying. Metoclopramide can cross the blood-brain barrier and thus may cause adverse effects related to dopaminergic blockade; domperidone does not cross the blood-brain barrier.

Dyskinesias
Dyskinesias are hyperkinetic movements related to dopaminergic effects that are greater or less than the therapeutic threshold. They are common with long-term...
levodopa therapy and have three patterns:

- **Off dystonia** occurs when levodopa concentrations are low and the SDR has dissipated. Dystonic states may be a manifestation of too little or too much levodopa; differentiating the two is important. Off dystonia occurs mostly in the early mornings, when plasma levodopa levels are low, and mostly involves the more affected side first.

- **Peak-dose dyskinesia**, which occurs during the SDR, is the most common type of dyskinesia and is related to peak plasma levodopa levels. It is characterized by stereotypic, choreic abnormal movements involving the head, neck, trunk, and limbs, and possibly hemidyskinesia in young-onset PD. Peak-dose dyskinesias are sometimes severe enough to be disabling.

- **Diphasic dyskinesias** are stereotyped, dystonic, or choreic movements that occur at the beginning of the SDR and again as the SDR dissipates. They predominantly affect the legs and spare the trunk, neck, and arms.

### Treatment of Off and Wearing Off

Increasing dopaminergic stimulation is the backbone of treatment of off periods or wearing off. The strategies to increase dopaminergic stimulation include addressing food and tolerance issues and adding a monoamine oxidase B (MAO-B) inhibitor or a catechol-O-methyltransferase (COMT) inhibitor such as entacapone or tolcapone to the regimen (Table). If the patient is already taking levodopa or a dopamine agonist, the dosage can be increased; or, levodopa can be added to a dopamine agonist regimen and vice versa.

#### Food and Tolerance

The patient should not take levodopa with protein-containing meals, particularly if his or her PD is at an advanced stage. If excessive nausea, vomiting, or lightheadedness prevents the patient from taking an adequate dose, adding carbidopa (up to 75 mg) to the regimen will be helpful.

#### MAO-B Inhibitors

By inhibiting one of the central dopamine catabolic pathways, MAO-B inhibitors (selegiline, rasagiline, and Zydis selegiline) prolong the half-life of dopamine in the brain and increase on time.

Improvement in off time with rasagiline is comparable to that seen with the COMT inhibitor entacapone. In an 18-week, double-blind trial of 687 patients randomized to receive once-daily rasagiline, entacapone, or placebo as an adjunct to levodopa, both rasagiline and entacapone reduced off time by 1.2 hours compared with placebo.

In a 26-week placebo-controlled study, rasagiline decreased off time by 29% when added to levodopa in patients with PD and motor fluctuations, compared with a 15% reduction in the placebo group. This study confirmed the benefit of adding rasagiline to the regimens of patients who were already optimally treated with levodopa, dopamine agonists, amantadine, anticholinergics, and entacapone before enrolling in the study.

An orally disintegrating selegiline (Zydis selegiline) tablet is particularly useful for patients who have difficulty swallowing. The bioavailability of Zydis selegiline is 80% compared with 10% for selegiline, resulting in faster absorption. Pre-gastric absorption of Zydis selegiline avoids extensive first-pass metabolism in the liver and, therefore, the concentration of amphetamine-like metabolites is much lower.

In a 3-month, placebo-controlled study of patients with PD who were experiencing levodopa-related motor fluctuations, Zydis selegiline was associated with a 2.2-hour reduction in the total number of off hours compared with 0.6 hours in the placebo group, and dyskinesia-free on hours increased by 1.8 hours.

The use of MAO-B inhibitors with tricyclic antidepressants or selective serotonin reuptake inhibitors has been reported to induce the serotonin syndrome by

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**TABLE**

Mechanisms for treatment of off and wearing off

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism</th>
<th>Comments</th>
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<tr>
<td>MAO-B inhibitors (rasagiline, selegiline, Zydis selegiline)</td>
<td>Inhibit a central dopamine catabolic pathway to prolong the half-life of dopamine</td>
<td>Increase on time, decrease off time; can induce serotonin syndrome if used with tricyclic antidepressants or SSRIs</td>
</tr>
<tr>
<td>COMT inhibitors (entacapone, tolcapone)</td>
<td>Block peripheral degradation of levodopa; prolong half-life and availability; tolcapone also blocks central degradation</td>
<td>Increase daily on time; tolcapone significantly improves off time, but risk of liver impairment requires monitoring every other week</td>
</tr>
<tr>
<td>Controlled-release levodopa</td>
<td>Provides more constant delivery of levodopa to the striatum</td>
<td>Variable absorption; more effective in patients with less severe wearing off</td>
</tr>
<tr>
<td>Dopamine agonists (pramipexole, ropinirole, apomorphine, bromocriptine)</td>
<td>Directly stimulate dopamine receptors</td>
<td>Adjunctive therapy that reduces wearing off; must be discontinued at first sign of side effects; ankle edema, hallucinations, somnolence, impulse control disorders</td>
</tr>
</tbody>
</table>

COMT = catechol-O-methyltransferase; MAO = monoamine oxidase inhibitor; SSRIs = selective serotonin receptor inhibitors
activation of 5HT1α and 5HT2 receptors. Serotonin syndrome is a potentially life-threatening accumulation of serotonin that can cause encephalopathy, severe rigidity of the legs, dysautonomia (diarrhea, mydriasis, and excessive lacrimation), myoclonus, hyperreflexia, and seizures.

**COMT inhibitors**

Catechol-O-methyltransferase inhibitors (entacapone and tolcapone) block peripheral degradation of levodopa. Tolcapone also blocks central degradation of levodopa and dopamine. These mechanisms increase central levodopa and dopamine levels and prolong levodopa half-life and bioavailability. Tolcapone has more powerful COMT inhibition than entacapone because tolcapone crosses the blood-brain barrier and inhibits the peripheral and central pathways of levodopa degradation. Use of COMT inhibitors can increase daily on time, but diarrhea is a common side effect and leads to withdrawal of these agents in about 3% of patients.

Tolcapone-treated patients show significant improvement in off time with improvement in motor fluctuations. Because tolcapone causes rare instances of fulminant hepatitis, liver function needs to be monitored every other week. For this reason, tolcapone should be reserved for patients in whom other treatments, including entacapone, have failed.

**Controlled-release levodopa**

Controlled-release levodopa was developed to provide more constant delivery of levodopa to the striatum. The benefit of controlled-release levodopa is only mild, however, as absorption of this formulation is variable. In advanced PD cases, the effects of controlled-release levodopa are more unpredictable than those with standard levodopa. Controlled-release levodopa is effective in patients with less severe wearing off, but it is not as effective in patients with a less predictable pattern of fluctuations.

**Dopamine agonists**

Dopamine agonists (pramipexole, ropinirole, apomorphine, and bromocriptine) have shown beneficial effects as adjunctive therapy to reduce wearing off. Side effects of dopamine agonists include ankle edema, hallucinations, somnolence, and impulse control disorders. These side effects should be discussed with patients before instituting therapy, and therapy should be discontinued if any of them occur.

In patients with advanced PD, pramipexole was shown to improve motor function during on and off periods, decrease the total off time, and decrease the severity of off time. Further, a larger reduction in the dosage of levodopa was possible in the pramipexole-treated patients than in the placebo-treated patients.

In a comparison of pramipexole with levodopa on the end point of motor complications of PD in 300 patients, the incidences of wearing off and dyskinesia were significantly lower in the patients randomized to pramipexole with follow-up over 4 years. Only 25% of patients initially treated with pramipexole exhibited dyskinesia compared with 54% of patients initially treated with levodopa. Forty-seven percent of patients in the pramipexole group experienced wearing off compared with 63% initially treated with levodopa. Pramipexole is available as tablets ranging from 0.125 mg to 1.5 mg in size. It is given in three divided daily doses with gradual increments of 0.25 mg three times a day every week. Pramipexole is now also available in an extended-release formulation for once-a-day dosing in tablets ranging in size from 0.375 mg to 4.5 mg.

**Ropinirole** adds clinical benefit in PD patients with motor fluctuations and also permits a reduction in the dosage of levodopa.

In one study, ropinirole monotherapy was compared with levodopa therapy in 268 patients with early PD. By the end of the 5-year study, 45% of the levodopa patients experienced dyskinesias versus 20% of the ropinirole patients.

Ropinirole is available as tablets ranging in size from 0.25 mg to 5 mg. It is now also available in an extended-release (XL) formulation, with tablet sizes ranging from 2 mg to 12 mg. Ropinirole XL is taken once a day.

**Bromocriptine** is an old ergot-derived dopamine agonist that has also been studied for monotherapy and add-on treatment in PD. Due to the potential risks of pulmonary, retroperitoneal, and heart valve fibrosis, bromocriptine is not commonly used.

**Apomorphine** was approved by the US Food and Drug Administration in 2004 as an acute, intermittent, subcutaneous injection for the treatment of hypomobility off episodes (end-of-dose wearing off and unpredictable on-off episodes) associated with advanced PD. Apomorphine has been shown to be beneficial in patients with unpredictable off periods. Its onset of action is 10 to 15 minutes, and the effects of each dose last for 60 to 90 minutes. The best tolerated dose is 4 mg to 10 mg. Apomorphine appears to be most useful as rescue medication in the refractory off periods with severe bradykinesia and unpredictable off periods.

**TREATMENT OF DYSKINESIAS**

Reduction of levodopa doses will reduce the frequency of dyskinesias, but at a cost of worsened parkinsonism and increased numbers of off periods. An alternative is to spread out the doses of levodopa (more frequent smaller doses), but this practice has not achieved good results. Replacing levodopa with dopamine agonists can also reduce the frequency of dyskinesias, but control
of PD symptoms is less optimal than with levodopa. Amantadine and clozapine both have been shown to reduce dyskinesias.

**Amantadine**
Amantadine is an N-methyl-d-aspartate antagonist with antidyskinesia effects. Metman et al demonstrated that amantadine reduced dyskinesia severity by 60%, without exacerbation of motor function, in a randomized placebo-controlled crossover study. Dose-response studies with amantadine have not been conducted, but 100 mg two or three times daily is used in practice. In some studies, a short duration of benefit has been a concern. Side effects of amantadine include leg edema, hallucinations, confusion, and rash.

**Clozapine**
Clozapine is an atypical antipsychotic that has been shown in open-label trials and a randomized, double-blind, placebo-controlled trial to reduce the duration and severity of levodopa-induced dyskinesias without worsening of parkinsonian features and with no change in motor fluctuation. No benefit of clozapine was observed during activation dyskinesia, however. Clozapine carries the inconvenience of weekly blood draws to monitor for the development of agranulocytosis, which occurs rarely.

**GAIT FREEZING**
Gait freezing, most commonly a manifestation of off states, causes substantial disability. It has been thought to occur as a result of a loss of noradrenaline due to locus ceruleus degeneration. Improvement in gait freezing has been shown with apomorphine and methylphenidate.

**CONCEPT OF CONTINUOUS DOPAMINE STIMULATION**
Short-acting dopaminergic drugs have the potential for nonphysiologic pulsatile stimulation of postsynaptic receptors, leading to motor complications. Continuous dopaminergic stimulation to prevent this pulsatile stimulation would theoretically avoid motor complications. Continuous dopaminergic stimulation can be achieved by using the extended-release formulation of ropinirole or pramipexole or by continuous delivery of levodopa or dopamine agonists. Several double-blind controlled trials have shown that treatment with long-acting dopamine agonists lowers the risk of motor complications compared with short-acting levodopa treatment.

In 2005, Stocchi concluded that in patients with advanced PD, a continuous infusion of levodopa was more effective in reducing motor complications than standard oral formulations. The reduction in motor complications was attributed to avoidance of low plasma levodopa trough levels; motor complications were not affected by relatively high plasma levodopa concentrations. The authors of this study speculated that if oral levodopa could be given “in a manner that mirrors the pharmacokinetic pattern of infusion,” it might be able to reduce motor complications.

This hypothesis led to an interest in treatment with levodopa plus entacapone. A regimen of levodopa-carbidopa-entacapone, four times daily at 3.5-hour intervals, was compared with levodopa-carbidopa in 747 patients with early PD over 134 weeks. Initiating levodopa therapy with levodopa-carbidopa in combination with entacapone did not delay the induction of dyskinesia compared with levodopa-carbidopa alone. In fact, levodopa-carbidopa-entacapone was associated with a shorter time to onset and an increased frequency of dyskinesia compared with levodopa-carbidopa.

**Potential future treatment options**
An intrajejunal pump system delivers a constant-rate infusion of levodopa. A double-blind study of this system is being conducted in the United States. Implantation of the system is an invasive procedure with the potential for infection, kinking dislocation, and occlusion and reposition of the catheter.

Miniature pumps for continuous subcutaneous delivery of apomorphine, currently available only in Europe, have been shown to reverse dyskinesias and motor fluctuations. Limitations of the minipumps are the development of red itchy nodules, ulcerations, and abscesses at infusion sites.

**Extended-release dopamine agonists**
Extended-release formulations of the dopamine agonists ropinirole and pramipexole are easy to administer, and they maintain therapeutic plasma levels for up to 24 hours. They are unlikely to replace stronger continuous dopamine stimulation with levodopa and apomorphine.

**SUMMARY**
Motor complications in PD result from progression of the disease and limitations of levodopa. Although the effects of levodopa on PD eventually wane, leaving patients vulnerable to motor complications, clinicians should not undertreat patients.

Effective options for the management of motor complications include prolonging the efficacy of levodopa through the use of selective MAO-B inhibitors and COMT inhibitors as adjuncts to levodopa or continuous dopaminergic stimulation achieved by the use of long-acting dopamine agonists or continuous intraduodenal levodopa.

Emerging therapies will be more efficient for continuous delivery of dopaminergic drugs. Pump delivery systems and extended-release formulations have shown promise.
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Nonmotor complications of Parkinson disease

**ABSTRACT**

Nonmotor manifestations are integral components of Parkinson disease (PD), and they often have a greater impact on disability and quality of life than the motor features that currently define the illness. Nonmotor features of PD, such as dementia, may be an intrinsic feature of the disorder and persist regardless of the medication state (ie, they continue to manifest in the "on" or "off" state); some nonmotor features, such as psychotic symptoms, may be iatrogenic complications of pharmacologic intervention for the treatment of the motor manifestations of PD. Iatrogenic complications, such as psychosis and impulse control disorders, may respond to modification of the PD treatment regimen at the risk of worsening motor symptoms. Thus, a balance must be struck between controlling nonmotor manifestations and motor features of the disease.

Although the definition of Parkinson disease (PD) is based on the presence of motor features, these are just the “tip of the iceberg.” Nonmotor manifestations are nearly ubiquitous in PD, with behavior problems often being the most malignant. Almost all patients with PD have nonmotor and neuropsychiatric features, including sleep disturbances, compulsive and impulsive behaviors, autonomic dysfunction, and psychosis.

The neuropsychiatric and behavioral features of PD can be classified as intrinsic features, which occur as part of PD, and iatrogenic features, which are complications that arise from treatments used to manage the motor symptoms of PD.

**DEMENTIA IN PD**

An intrinsic nonmotor feature of PD is dementia, which occurs at a rate four to six times greater in patients with PD than in age-matched controls without PD. The prevalence of dementia in PD varies among studies and depends on the demographics of the population being studied. The cross-sectional prevalence of dementia is 40% in patients with PD.

Dementia is a burden to the caregiver, the patient, and society. Cognitive and behavioral symptoms in patients with PD are the greatest contributors to caregiver distress. Dementia and associated behavioral symptoms (ie, hallucinations) hasten nursing home placement, contributing to the financial burden of caring for patients with PD. The risk of mortality is increased when dementia develops.

At least one medication has shown promise in managing PD dementia. In a pivotal trial of the cholinesterase inhibitor rivastigmine, involving more than 500 patients with PD dementia, the patients randomized to rivastigmine had a 3-point improvement on the primary outcome measure—the mean change from baseline in the Alzheimer’s Disease Assessment Scale-Cognitive Subscale—compared with those randomized to placebo (Figure 1). This trial led to US Food and Drug Administration approval of rivastigmine for the treatment of PD dementia.

**PSYCHOTIC SYMPTOMS IN PD: AN EFFECT OF EXCESS DOPAMINE STIMULATION**

Most of the complications observed in PD can be explained by the dopamine effect of medications and by dopamine deficiencies. An excess of dopamine stimulation caused by administration of prodopaminergic agents manifests as dyskinesias, hallucinations, or delusions. Withdrawal of levodopa will reverse these complications but leads to dopamine deficiency and thus a worsening of PD symptoms. Most patients with PD will tolerate mild dyskinesias or hallucinations if their PD symptoms are well controlled.

The hallucinations in PD tend to be visual as opposed to auditory (as in schizophrenia). They are usually benign and involve figures of people, furry animals, or complex scenes. About 10% to 40% of hallucinations...
in PD are secondary auditory hallucinations, which tend to be nondistinct, non-paranoid, and often incomprehensible (ie, voices in a crowd).

In the same way, the delusions experienced in patients with PD are distinct from those in schizophrenia. The delusions in PD are usually paranoid in nature and involve stereotyped themes (ie, spousal infidelity, feelings of abandonment) rather than the grandiose delusions that are common in schizophrenia.

The reported prevalence of psychotic symptoms in PD, including hallucinations and delusions, ranges from 20% to 50%.8,9 Auditory hallucinations are a feature in about 10%, and they usually occur with visual hallucinations. Less common are delusions and hallucinations with loss of insight, which are more likely with increasing severity of dementia.

Once a PD patient experiences hallucinations, they are likely to continue. In a 6-year longitudinal study, the prevalence of hallucinations increased from 33% at baseline to 55% at 72 months.10 Persistent psychosis was found in 69% of participants in the Psychosis and Clozapine in PD Study (PSYCLOPS) with 26 months of follow-up.11

High caregiver burden
Psychotic symptoms in PD are associated with high caregiver stress and increased rates of nursing home placement. Goetz et al12 showed that PD patients with psychosis had a much greater risk of nursing home placement than those without psychosis. The prognosis for PD patients in extended-care facilities is worse for those with psychotic symptoms.13

Management of psychotic symptoms
The first step in managing psychosis in PD is to rule out other causes of changes in mental status, such as infection, electrolyte imbalance, or introduction of new medications.

Adjusting anti-PD medications to a tolerable yet effective dose may help to reduce the incidence and severity of psychotic complications. If necessary, selective discontinuation of anti-PD medications may be tried in the following sequence: anticholinergics, amantadine, monoamine oxidase B inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitors, and levodopa/carbidopa.

If motor symptoms prevent dosage minimization or discontinuation of some medications, then the addition of an atypical antipsychotic medication should be considered. Before the advent of atypical antipsychotics, the management of psychosis and hallucinations in PD was unsatisfactory, reflected by a mortality of 100% within 2 years among psychotic PD patients placed in nursing homes compared with 32% among age-matched community dwellers.13 The introduction of atypical antipsychotics has improved survival among PD patients with psychosis. In one study, mortality over 5 years was 44% among PD patients taking long-term clozapine for the treatment of psychosis.14 Recurrence of psychosis is rapid (within 8 weeks) even when PD patients are slowly weaned from atypical antipsychotics.15

Receptor affinities differ among antipsychotics. Because dopamine has been implicated as the principal neurotransmitter in the development of PD psychosis, atypical antipsychotics, with milder dopamine-blocking action, have played a central role in the treatment of PD psychosis. The dopamine D2 receptor is the main target for conventional antipsychotic drugs to exert their clinical effects. Atypical antipsychotics have different affinities for the D2 receptors.16

Occupancy of D2 receptors with atypical antipsychotics is 40% to 70% (risperidone and olanzapine have higher affinity for the D2 receptor than clozapine and quetiapine), and affinity for 5-HT2A receptors can be as high as 70%. This affinity for 5-HT2A receptors relative to D2 receptors may be important for therapeutic efficacy of the atypical antipsychotics. Antagonism of muscarinic, histaminergic, noradrenergic, and other serotonergic receptors also differs among the atypical antipsychotics.

Clozapine remains the gold standard atypical antipsychotic agent, based on results from three relatively small (N = 6 to 60) double-blind, placebo-controlled studies in PD patients with dopaminergic drug-induced psychosis.17-19 Quetiapine improved psychotic symp-
Depression

Challenges in the management of depression in PD include recognition of depression and distinguishing depressive disorders from mood fluctuations. Whereas a depressive disorder lasts from weeks to years and can occur at any stage of illness, mood fluctuations can change many times daily and appear as nonmotor manifestations during the “off” medication state. Mood fluctuations occur mostly in patients who have developed motor fluctuations. The implication for treatment is that the treatment strategy for a depressive disorder is antidepressant therapy, whereas the strategy for mood fluctuations in PD is to increase the levodopa dose.

Recognition of depression in PD is confounded by the depression criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; many of these criteria can be intrinsic features of PD itself—for example, anhedonia, weight/appetite loss or gain, insomnia or hypersomnia, psychomotor retardation, and fatigue. Questions such as “are you feeling sad” or “are you feeling blue” may be superior to questions about associative symptoms when evaluating PD patients for depression.

The value of rating scales also should not be overlooked. Shulman et al.25 found that the use of standardized rating scales is superior to routine office assessment by neurologists in recognizing depression in PD patients; in more than 50% of routine office assessments, neurologists missed a diagnosis of depression (Figure 2).

Most of the medications used for the treatment of depression also work well for depression in patients with PD. Double-blind controlled studies have demonstrated superiority of nortriptyline, citalopram, desipramine, and pramipexole over placebo in improving mood.26–29

Apathy

The overlap between apathy and depressive symptoms can also complicate recognition of apathy, which can be described as a lack of motivation or failure to initiate goal-directed behavior. Apathy involves three domains:20

- Cognitive: expressed as a loss of interest in new experience or a lack of concern about a personal problem
- Diminished affect: flattened affect or a lack of reaction to positive or negative events
- Final: diminished goal-directed cognition, as indicated by a lack of effort or requiring others to structure activities

Unlike depression, which is similarly representative of PD and other episodic conditions such as dystonia, apathy is more common in PD than in dystonia. In fact, the occurrence of apathy alone distinguishes PD from dystonia. Apathy in PD has no known treatment. If it is associated with depression, apathy may respond to antidepressants.

MOOD DISTURBANCES IN PD

Depression and apathy occur more frequently in patients with PD than in those who do not have PD.
Repetitive transcranial magnetic stimulation (rTMS) manipulates activity in specific brain neural circuits through the skull to induce changes in behavior. Some studies suggest that modulation of behavior may last beyond the actual stimulation. A randomized, sham-controlled trial of rTMS over the middorsolateral frontal cortex has been conducted with the primary aim of improving apathy in PD. Unfortunately, while patients who were randomized to rTMS experienced some improvement in apathy during the study, the improvement was not significantly different from that observed in patients who received sham treatment.31

**IMPULSE CONTROL AND COMPULSIVE DISORDERS IN PD**

Impulse control disorders are characterized by the inability to resist an urge to act; the resulting irrational desire to pursue self-gratification may inflict suffering on friends and relatives that compromises relationships and impairs social- and work-related functioning.

Examples of impulse control disorders in PD are pathologic gambling, hypersexuality, compulsive shopping, excessive spending, and binge eating. Patients taking dopamine agonists are two to three times more likely to develop impulse control disorders than those receiving other treatments for PD. Dopamine agonists with relative selectivity for D3 receptors have been implicated in impulse control disorders in PD because D3 receptors are abundant in a region of the brain (ventral striatum) associated with behavioral and substance addictions. Higher levodopa dosages were also associated with impulse control disorders.

Factors associated with impulse control disorders in PD are young age, being single, a family history of impulse control disorders, and levodopa treatment.12 Modifications to dopamine agonist or levodopa therapy are important in the treatment of dopamine agonist–induced impulse disorders.

Compulsive disorders have been described as a class distinct from impulse control disorders and involve repetitive stereotypes and well-ordered acts to decrease inner anxiety and avoid harm. Punding is the engagement of stereotyped behaviors that are repeated compulsively—for example, repetitive manipulation of technical equipment; continual handling, sorting, and examining of objects; grooming; and hoarding. The punder has poor insight into the disruptive and senseless nature of his or her acts. Punding has consistently been related to dopaminergic therapy. Its prevalence in PD patients on dopaminergic therapy ranges from 1.4%33 to 14.34 An improvement in behavior is observed with a reduction in dosage or discontinuation of levodopa.

Pathologic gambling, or the inability to control gam-

**REFERENCES**


**SUMMARY**

Dementia, psychotic symptoms, mood disturbances, and impulse control disorders are important nonmotor manifestations of PD that present management challenges. Some of these manifestations are intrinsic to PD, and some are complications of therapies used to treat the motor manifestations of PD.

Dementia and psychotic symptoms extract a considerable toll on the patient, caregivers, and society. Psychotic symptoms generally manifest as hallucinations (mostly visual) and other sensory disturbances. Initial management involves adjustment of anti-PD medications. The use of atypical antipsychotic drugs has been shown to improve survival among patients with PD. Clozapine is the preferred agent.

Mood disturbances such as depression and apathy may be difficult to diagnose. Depression may be treated similarly to depression unassociated with PD.

Dopamine agonists and levodopa have been associated with impulse control disorders in PD. Compulsive disorders, which are distinct from impulse control disorders, may improve with reduction or discontinuation of levodopa therapy.


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ABSTRACT

Deep brain stimulation (DBS) is used as a treatment for movement disorders. Unlike ablative procedures, DBS is reversible and adjustable. It is approved in the United States for treatment of Parkinson disease (PD), dystonia, and tremor. This surgical procedure is considered safe and effective for the management of the motor symptoms of these disorders, although it does not cure the underlying conditions. Potential complications of DBS surgery include intracranial hemorrhage, infections, and complications related to the hardware. There may also be complications related to stimulation or programming, although these are usually associated with dosages of dopaminergic medications and are reversible. DBS is used for conscious sedation with awake evaluation during intraoperative physiologic testing. Typically, the procedure is performed with stereotactic image guidance, using computed tomography or magnetic resonance imaging (MRI) for targeting. Surgery can be accomplished with stereotactic frames or frameless systems. Recently, intraoperative MRI guidance has become available and is an alternative to the traditional surgical procedure, allowing for implantation of the DBS device under general anesthesia.

Deep brain stimulation for movement disorders: Patient selection and technical options

Deep brain stimulation (DBS) is also approved for managing primary generalized dystonia and torticollis under a humanitarian device exemption.

Deep brain stimulation has largely replaced ablative procedures such as thalamotomy and pallidotomy. While ablative procedures can be effective for the symptoms of movement disorders, they cause a permanent lesion in the targeted nuclei and are therefore not reversible. DBS is considered safer because it can be adjusted over time and the location of the leads can be revised.1 On the other hand, regular maintenance of implanted hardware may be considered a disadvantage of DBS.

HARDWARE AND TARGETS

Implantation of a deep brain stimulator is the most common surgical procedure performed in the United States and industrialized world for the management of advanced movement disorders. These procedures are US Food and Drug Administration (FDA)–approved for the management of the symptoms of Parkinson disease (PD) and essential tremor. Deep brain stimulation consists of permanently implanted neurostimulation systems. The battery-powered pulse generators typically last for several years but require multiple replacements during a lifetime. In addition, if other hardware components fail, surgical revision may be required to maintain treatment efficacy. Surgery involving implantation of hardware carries a higher risk of infection than does a nonimplantation procedure. If infections occur, removal of the hardware is often required, with reimplantation performed after the infection clears. In addition, the expense of DBS hardware may limit availability in some cases.

Three components

Permanently implanted DBS devices have three components: the DBS lead, which is inserted into the brain and extends to the outside of the skull; the implantable pulse generator, typically located in the infraclavicular area; and an extension cable that connects the two components (Figure 1). Patients may have unilateral or bilateral lead implantation and unilateral or bilateral implantation of pulse generators. A single generator may be connected to both brain leads. Patients also have the option of receiving either a nonrechargeable or a rechargeable pulse generator. The advantage of the latter is longer intervals between battery replacement surgery (up to 9 years). However, these require more maintenance by the patient, who needs to periodically recharge the generators at home using a wireless charg-
ING unit. The recharging procedure may be time-consuming and difficult for patients who are challenged by new technologies. In our experience, most patients with PD and tremor prefer nonrechargeable pulse generators.

Target nuclei
Several nodes or nuclei can serve as targets for DBS. In patients with PD, the most common surgical target is the subthalamic nucleus (STN), either unilaterally or bilaterally. The globus pallidus pars interna (GPI) is also a viable target and is preferred for some patients with PD. The most common target for managing essential tremor is the ventral intermediate nucleus (VIM) of the thalamus, which can also be the target of choice for patients with tremor-predominant PD. However, the GPI and STN are usually preferred over the VIM in patients with PD because stimulation of these targets can relieve symptoms other than tremor, such as rigidity and bradykinesia. Bilateral stimulation of the GPI is the most frequent approach in patients with generalized torsion dystonia and torticollis, although the STN and thalamic nuclei (off-label) are also considered options.

PATIENT SELECTION
Patients are evaluated in our center at Cleveland Clinic by a multidisciplinary team that includes a movement disorder neurologist, a subspecialized neurosurgeon, a movement disorder neuropsychologist, and a psychiatrist with special interest in the behavioral comorbidities of movement disorders. Neuroimaging is included in this assessment. We have also included physical therapy as part of the initial evaluation in order to gain insight into the patient’s limitations and develop rehabilitation strategies that may enhance the outcomes of surgery or provide alternatives should surgery not be indicated. This evaluation provides extensive data that are then reviewed by the team in a conference dedicated to discussing candidacy for DBS or options for managing the symptoms of advanced movement disorders. Behavioral and cognitive issues are assessed in detail and, in our experience, are the most common reasons for not recommending DBS.

An important part of the evaluation of patients with PD is a formal test with rating of the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS) with the patient off medications for 8 to 12 hours and then after a test dose of levodopa. At our center, this off/on test is videotaped so that the responsiveness of individual symptoms to levodopa can be reviewed later in conference.

Risk of cognitive decline
While DBS is considered safe and effective, there is a risk of cognitive decline in some patients. In most patients, long-term stimulation-related cognitive decline may be detected with formal measures but is not clinically significant and is outweighed by the motor and quality-of-life benefits of surgery. In some patients, long-term cognitive decline can be significant and can limit function. Cognitive neuropsychlogic testing provides valuable information in this regard. Patients with preserved cognitive function seldom experience significant decline with DBS while those with substantial baseline impairment are thought to be at greater risk. Patients who meet criteria for dementia are usually not considered candidates for DBS, but exceptions exist. Transient perioperative cognitive difficulties are more common than persistent deficits, and typically resolve within a few weeks (see “Complications of deep brain stimulation,” page S22).

Benefits in Parkinson disease
Deep brain stimulation can address several symptoms of PD but with varying effects. Tremor, rigidity, and bradykinesia usually improve substantially. Gait has a more variable response, and balance is typically refractory. A general rule is that symptoms that improve with a single dose of levodopa should also improve with DBS. (Tremor, however, will most often respond to DBS even if refractory to medication.) Good candidates for surgery typically have a greater than 30% improvement in UPDRS motor score with levodopa challenge, but sometimes, improvement in the total score is less informative than evaluation.
of the effects of levodopa on particular symptoms. Treatment effects can be compared with the patient’s expectations for surgery in order to infer whether the goals for symptom improvement are realistic.

**Treatment outcomes depend on etiology**

After programming, DBS can provide PD symptom control similar to that of medication “on time,” but with fewer on-off fluctuations and less on-time dyskinesia. Good surgical candidates are patients who once responded well to dopaminergic medications but who, after several years with the disease, present with increased duration of “off time,” unpredictable duration of on time, and medication side effects such as on-time dyskinesia. Patients who do not respond well to levodopa even in subscores of the UPDRS may not be good candidates for DBS, and in some cases the diagnosis itself needs to be reviewed.

Deep brain stimulation can improve quality of life and alleviate symptoms of essential tremor. Tremor control is best for the upper extremities and tends to be better for distal tremors than for proximal ones. Patients who are good candidates for surgery often have severe tremors. A substantial improvement in these symptoms often has a dramatic, positive effect on work and quality of life. In some patients, surgery is considered for mild tremor if it seriously disrupts the patient’s lifestyle or occupation and cannot be well controlled with medications. Often, in these cases, tremor that appears relatively mild to the examiner is significantly limiting for the patient.

Very severe and proximal tremor is more refractory, though it may also improve. The changes can be well documented with objective measures. In these cases, however, residual tremor can still be moderate to severe and can be functionally limiting. Head or vocal tremors are typically refractory. They may be improved with bilateral implantation, but this cannot be accurately predicted. Patients who present with head-only or head-predominant tremor are thought to be less likely to benefit than those with limb tremor. Nonetheless, tremors of the head can severely impair quality of life. Because there are few other treatment options, some patients choose DBS with the understanding that the outcome is uncertain and the benefit may be limited.

Tremor resulting from multiple sclerosis or other causes can be medically refractory and disabling. In our experience, DBS can be an off-label option for managing secondary tremors and good outcomes have been observed. However, outcomes are much less predictable and tremor control less effective than in patients with essential tremor.

Patients with primary generalized dystonia can be considered candidates for DBS and may experience improved symptom control and quality of life. Patients with the DYT1 mutation are more likely to respond well to DBS, as are those with other forms of primary generalized dystonia. In contrast to that seen in patients with PD and tremor, symptomatic improvement is frequently not observed during intraoperative testing. Several months of stimulation and programming may be required before significant improvements are detected. Surgery can also be considered for off-label use in the treatment of patients with secondary dystonia—such as that following injury or associated with cerebral palsy—but outcomes are less predictable and usually more limited. A possible exception may be seen in cases of tardive dystonia, for which there is increasing evidence for the effectiveness of DBS. This remains an off-label use of DBS.

**Realistic expectations**

An important aspect of the multidisciplinary evaluation includes a discussion of the expectations for surgery, the risks, and the requirements for postoperative care. As discussed above, DBS is reversible and adjustable, so outcomes depend not only on accurate implantation of the hardware but also on postoperative programming. Also, monitoring and maintenance of the implanted hardware are required in these patients. It is important that patients and families appreciate the fact that specialized, long-term postoperative follow-up is as much a part of the treatment as is the implantation itself.

**UNILATERAL VERSUS BILATERAL DBS**

Most patients with generalized dystonia undergo bilateral DBS. However, patients with PD or essential tremor may receive bilateral, staged, or unilateral implants. Some patients with PD present with either near-complete predominance of symptoms on one side or with symptoms that affect mostly the dominant extremity. In these patients, unilateral implantation is often recommended because it has less risk than the bilateral approach and may be sufficient to address the most limiting symptoms.

As the disease advances, an additional surgery may be required to accomplish bilateral symptom control. Nevertheless, we do not routinely recommend preventative implantation because it is not known whether second-side symptoms will become severe enough to require it. This strategy allows for deferring surgical risk, which is in itself advantageous. In our experience, bilateral implantation is often recommended to PD patients who present with symptoms such as freezing of gait.

Patients who have essential tremor often present with bilateral symptoms. Although many patients will indicate that they need symptom relief on both upper extremities in order to perform activities of daily living, our practice is to recommend surgery on one side at first and to suggest the patient consider contralateral implantation after weeks or months. Bilateral implantation may carry a risk for dysarthria and the risk is thought to be reduced.
DEEP BRAIN STIMULATION

COMPLICATIONS OF DEEP BRAIN STIMULATION

Potential complications of deep brain stimulation (DBS) may be related to the surgery, the hardware, or stimulation.

Surgical complications
Surgical complications include intracranial and intracerebral hemorrhage, infection, misplacement of the DBS leads, or suboptimal placement of the leads. Intraoperative or postoperative hemorrhage is the most dreaded complication of DBS. While many smaller hemorrhages are asymptomatic or only transiently symptomatic, larger hemorrhages can be devastating. Hemorrhages may occur as the result of laceration to intracerebral vessels during microelectrode recording or lead implantation. In some cases, hemorrhages can be delayed and related to venous infarction or to clotting disorders. For treatment of Parkinson disease, either the globus pallidus pars interna (GPi) or the subthalamic nucleus (STN) can be targeted. Surgery on the GPi carries a greater hemorrhagic risk than does that on the STN. The risk of perioperative, cardiovascular, pulmonary, or other medical complications varies with age, comorbidities, and medical history.

Hardware complications
Hardware complications include migration of the leads, DBS lead failure or failure of any component of the system, and pain over the hardware. Battery failure can be addressed by replacing the generators prior to the estimated expiration.

Erosion of the subcutaneous portions of the hardware through the skin is also a concern and thought to be more common in patients with a very low body mass index. Erosion can happen at any time after implantation. Infection requires complete or partial removal of the DBS system.

Stimulation-related complications
All patients will experience some stimulation-related side effects during DBS programming. Stimulation signals with amplitudes greater than those required to achieve symptom control will affect neighboring structures—such as the internal capsule—and cause unintended effects. One of the goals of programming is to identify these thresholds and to set stimulation at amplitudes that do not cause intolerable side effects. Stimulation-related adverse effects are reversible with amplitude adjustments. Dyskesesia, worsening of axial symptoms (freezing, balance, and gait disturbance), speech disturbance, involuntary muscle contractions, paresthesia, and diplopia are among the common stimulation-related and transient side effects. Stimulation-induced dyskinesia is frequently managed with a reduction in the dosage of dopaminergic medications. In fact, in order to control symptoms with fewer medication side effects, programming of DBS—particularly the first few sessions—is performed along with changes in levodopa doses.

if bilateral procedures are staged. Although high rates of dysarthria have been reported following bilateral surgery for tremor, its occurrence has been infrequent in our experience with bilateral staged DBS. Benefits of treating tremor in the dominant extremity usually exceed those of treating nondominant tremor, so most patients prefer that the dominant side be the first one treated.

TECHNICAL OPTIONS

There are several technical options for implantation of DBS systems. Stereotactic procedures rely on co-registration of preoperative imaging with external and internal fiducials, or points of reference. Targeting of the intended structures is performed by combining direct and indirect methods. Direct methods rely on identification of the target structures with imaging, such as visualization of the STN and GPi on preoperative magnetic resonance imaging (MRI). Indirect targeting relies on cadaveric anatomic atlases and coordinate systems that infer the location of the intended structures in relation to anatomical points of reference.

Frame-based systems
In the most common approach to DBS surgery,7 stereotactic frames are placed over the patient’s head and secured with pins. The frame becomes the fixed point of reference for accurate stereotactic surgery and must remain in place for the duration of the procedure. Computed tomography or MRI is then performed with the frame in place, so that the images are co-registered with the fiducial points of the stereotactic frame. The targets are then selected for surgery and trajectories are chosen based on anatomic structures. The patient is positioned supine and the frame and head are secured to the operating table. The coordinates calculated by the clinical workstations are then set to the stereotactic frame and arc. The stereotactic arc (Figure 2) is attached to the base of the frame and the entry points of the leads—where the burr hole will be placed—are marked on the skin and then on the skull. Once the burr hole and opening of the meninges are completed, the targeting cannulae are inserted. The microelectrode system is then mounted for recording of the target area and subsequently for final lead implantation.

Frameless systems
The workflow and overall surgical procedure for implantation of DBS with frameless systems are similar to those of the frame-based procedure. However, instead of fixing the head to a rigid frame that prevents head motion,
a lighter-weight, frameless system is fixed to the head and moves with it (Figure 3). First, metal screws and fiducials are fixed to the head under local anesthesia or sedation. Preoperative imaging is then acquired with the fiducials in place and the surgical plans are completed in the same fashion as for frame-based surgery. The patient is then placed supine on the operating table and the frameless system is attached to the head with the aid of image guidance, in the location determined by target and trajectory planning.

The key advantage of the frameless system over the frame-based system is greater mobility of the head. Another important advantage is easier access to the airway, should an emergency situation occur. In our practice, patients with experience of both frameless and frame-based systems did not report significantly less discomfort with the frameless system.

The frameless system also has disadvantages, including less secure fixation of the head, which can add risk to the procedure. In addition, because of its lightweight, plastic construction, it provides less robust support to the instrumentation entering the brain than do metallic head frames and, in some cases, there is less flexibility for adjusting targets if needed during surgery. In addition, frameless systems are nonreusable and represent a substantial additional cost.

**Microelectrode recording**

Physiologic verification of anatomic targets identified by imaging can be accomplished with microelectrode recording (MER). This technique involves placing fine, high-impedance electrodes through the target area, so that anatomic structures can be recognized by characteristic electrical activity of individual neurons or groups of neurons. The locations of the structures are identified and the lengths of the electrode trajectories through the different structures—as well as the gaps between these structures—are recorded. The distances are then compared with the anatomy and a best-fit model is created to infer the location of the trajectory in the target area. Additional MER penetrations are made in order to further delineate the anatomy. Once a location for implantation has been selected, the DBS lead is inserted into the target area.

**Electrode implantation**

Lead implantation is often performed under fluoroscopic guidance in order to ensure accuracy and stability. When implanted, the electrode may cause a microlesional effect, manifested by transient improvement in symptoms.

The DBS leads are then connected to external pulse generators and assessed for clinical benefits and
side effects. Amplitude, pulse width, and frequency are adjusted to test the therapeutic window of stimulation (clinical improvement thresholds versus side effect thresholds). Some PD patients develop dyskinesia during test stimulation, which may be a positive indicator for lead location. If good effects and a therapeutic window are observed, the location of the lead is considered to be satisfactory and the procedure is completed.

**Pulse generator implantation**

During the final step of surgery, performed under general anesthesia, the pulse generator is implanted. The extension cable that connects the DBS lead to the implantable pulse generator is tunneled subcutaneously, connecting the DBS lead to the pulse generator in the chest.

**Intraoperative, real-time MRI stereotaxis**

Real-time intraoperative MRI has become available for DBS implantation with devices recently cleared for use by the FDA. The procedure, typically performed in a diagnostic MRI suite, uses MR images acquired during surgery to guide DBS lead implantation in the target area and to verify implantation accuracy.⁸

**REFERENCES**


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Dystonia is a movement disorder in which involuntary sustained muscle contractions cause twisting movements that place the body in abnormal, sometimes painful, positions. Dystonia is believed to arise from an abnormality in the basal ganglia and an inherent or acquired defect in the processing of neurotransmitters.1

Dystonia is uncommon, although its exact prevalence is unknown. Nutt et al concluded that at least 250,000 people were affected by idiopathic dystonia in the United States, but prevalence is likely higher because misdiagnosis is not uncommon.2 A more recent European study found the prevalence of primary dystonia in the general population aged 50 years or more to be 732 per 100,000.3 The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group found that the estimated prevalence of cervical dystonia was 50 to 200 per 1 million individuals.4 Also known as spasmodic torticollis, this is the most commonly diagnosed form of focal dystonia.

ABSTRACT

Dystonia, an uncommon movement disorder that causes sustained muscle contractions and painful body positions, is a difficult diagnostic challenge; misdiagnosis is common. Classification may include etiology, area of physical involvement, or age of onset. Bodily distribution is varied, and dystonias can present as primary (genetic) or secondary (caused by other disease processes or use of neuroleptic drugs). Although there is no cure, the use of botulinum toxins for chemodenervation provides symptomatic relief and is considered the treatment of choice in focal dystonia. The dose of botulinum toxin may be titrated to provide significant relief for 12 weeks or more.

CLASSIFICATION OF DYSTONIA

Accurate classification of dystonia is important, since this informs approaches to management as well as prognosis. The three most important means by which dystonia is classified are (1) etiology, including primary dystonia, which encompasses a variety of genetic variables, and secondary dystonia; (2) bodily distribution of symptoms; and (3) age at onset.

Etiology

Most primary or idiopathic dystonia appears to be hereditary. Early-onset primary dystonia is most frequently caused by a mutation in the DYT1 gene, although other genetic mutations are possible.5 Patients with primary dystonia have no other underlying disorder; involuntary muscle contractions are the sole symptom. A thorough history should include a review of perinatal and early developmental history, prior neurologic illness, and exposure to drugs known to cause acquired dystonia. Physical examinations (encompassing intellectual, pyramidal, cerebellar, and sensory domains) and laboratory tests reveal no specific cause for the dystonic symptoms. Primary dystonia is also most frequently action-induced; at rest, the affected body region may appear to be normal.

Secondary dystonia occurs as a symptom of another disease process. Multiple sclerosis or any one of several hereditary neurologic disorders, such as Wilson disease, may be implicated. Secondary dystonia also may result from trauma to the brain, as might occur during an automobile accident; from heavy-metal or carbon monoxide poisoning; or as an adverse effect of medication. It may be psychogenic or related to Parkinson disease or Parkinson-plus syndromes, a group of neurodegenerative disorders with parkinsonian features. Tardive dystonia, the most common adult form of secondary dystonia, may occur following exposure to certain neuroleptic drugs; tardive dystonia is a type of tardive dyskinesia that describes any involuntary neurologic movement disorder.

Bodily distribution

Dystonia is further classified by location of symptoms. Focal dystonias, which are usually primary dystonias, describe symptoms that are limited to a region of the body, such as a specific arm. There are several variations.
Cervical dystonia affects the head and neck, is the most common adult-onset dystonia, and affects more women than men. Blepharospasm, or involuntary contractions of the eyelids, potentially leads to extended eye closure and functional blindness and often involves other facial muscles. Laryngeal dystonia affects the muscles in the larynx. Limb dystonia, such as writer’s or musician’s cramp, affects muscles in the arm, hand, leg, or foot. Limb dystonia is often task-specific action dystonia, and can be primary or secondary.

Segmental dystonia describes a group of involved muscles that are contiguous, such as cranial to neck to cervical to arm. Oromandibular dystonia, affecting the face, mouth, and jaw, often with unusual tongue movements (ie, lingual dystonia), is a type of segmental dystonia, although some consider it a focal dystonia. Meige syndrome is the combination of blepharospasm and oromandibular dystonia. Certain limb and cranial dystonias are considered segmental dystonias. Dystonia that affects two or more noncontiguous muscle groups in different parts of the body is multifocal. Hemidystonia describes unilateral symptoms.

Symptoms that have advanced from a focal presentation to affect additional regions of the body characterize generalized dystonia. The symptoms potentially advance to include the trunk and limbs. The muscular contractions are usually sustained, are often both repetitive and painful, and worsen with activity. In severe cases, muscular contractions may occur even while resting. Early-onset myoclonus dystonia is a generalized hereditary dystonia whose symptoms include dystonic contractions of the neck and shoulders and rapid jerking movements. Of note diagnostically, early-onset dystonia in a leg typically begins at age 8 to 9 years and is more likely than other early-onset presentations to progress to generalized dystonia. Early-onset dystonia that begins in an arm typically presents later, at age 12 to 14 years, and is less likely to progress to generalized dystonia. Late-onset dystonia (> 27 years of age), by contrast, rarely begins in a leg and tends to remain either focal or segmental.

**Age of onset**

A third useful classification scheme identifies early-onset (childhood to young adult) and late-onset varieties of dystonia.

**THE DIAGNOSTIC CHALLENGE**

Accurate diagnosis of dystonia is challenging because of its relative rarity and the variety of etiologies that pertain to this heterogeneous family of disorders. Patterns of inheritance are not straightforward and primary dystonia can be difficult to diagnose even with the benefit of genetic testing. There is no identifiable pathologic abnormality in many patients, and negative genetic tests do not necessarily mean that the dystonia is not primary. In the face of these challenges it is not surprising that dystonia is frequently misdiagnosed (Table 1). Nevertheless, certain findings can guide the diagnosis toward primary or secondary dystonia.

**Consider primary dystonia** if perinatal and developmental histories, intellect, strength, and perception of sensations are normal. There should be no prior history of neurologic illness or exposure to neuroleptic drugs whose adverse effects include secondary dystonia. In primary dystonia, diagnostic studies are negative and dystonia is the only symptom. If onset of symptoms is associated with activity, then primary dystonia should be considered. In the case of early- or late-onset limb dystonia, testing should be performed for the \( \text{DYT1} \) gene. If the results are negative, then a trial for dopa-responsive dystonia should be undertaken with levodopa.

**Consider secondary dystonia** if the patient has been exposed to neuroleptic drugs, symptoms are distributed unilaterally, or the presentation is unusual for age or distribution of symptoms. For example, cranial dystonia in a child would raise the index of suspicion for secondary dystonia. If tardive dystonia is part of the differential diagnosis, consider magnetic resonance imaging (MRI), serum ceruloplasmin measurement, or slit-lamp diagnostic testing. Suspicion of a structural lesion affecting the central nervous system warrants examination with MRI, computed tomography, or angiography. Certain metabolic and neurologic hereditary disorders cause secondary dystonia, in which case dopa-responsive dystonia should be ruled out. Psychometric testing should also be considered.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Type of dystonia</th>
<th>Misdiagnosed as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>Tic, dry eye syndrome</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>Arthritis, stiff neck, subluxation of cervical vertebrae, tumor of posterior fossa</td>
</tr>
<tr>
<td>Dystonia, all forms</td>
<td>Stress, anxiety, nervousness; psychogenic disorders</td>
</tr>
<tr>
<td>Laryngeal dystonia</td>
<td>Laryngitis, sore throat, vocal abuse</td>
</tr>
<tr>
<td>Oromandibular dystonia</td>
<td>Temporomandibular joint disorder</td>
</tr>
<tr>
<td>Writer’s cramp</td>
<td>Carpal tunnel syndrome, muscle strain, lateral epicondylitis</td>
</tr>
</tbody>
</table>

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SYMPTOMATIC TREATMENT WITH CHEMODENERVATION

In the absence of a cure, treatment options for dystonia are necessarily symptomatic and supportive. Titratable chemodenervation agents are injected directly into the muscle or motor nerve, temporarily weakening the local muscle and easing dystonia symptoms. Chemodenervation agents include phenol, ethyl alcohol, and botulinum toxin types A (BTX-A; onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) and B (BTX-B; rimabotulinumtoxinB).

Phenol and ethyl alcohol injections targeted perineurally or as a motor point block have been employed for dystonia and cause nonselective tissue destruction, muscle necrosis, and highly variable durations of response. Perineural microcirculation may be damaged, possibly leading to long-term defects.

Clostridium botulinum bacteria produce seven serologically distinct neuroparalytic toxins. They are the most powerful such toxins currently known and temporarily prevent acetylcholine vesicles from docking into the presynaptic neuromuscular junction. Use of BTX-A for treatment of dystonia was recommended in a National Institutes of Health consensus statement in 1990. It has been studied for a variety of dystonias, including blepharospasm, hemifacial spasm, laryngeal dystonia, oromandibular dystonia, and cervical dystonia, among other focal dystonias. Lew et al reported in 1997 on the successful use of BTX-B for cervical dystonia in a double-blind, single-treatment study, and confirmatory studies followed.

Varying indications for botulinum toxin

US Food and Drug Administration–approved indications for the toxins vary. The three BTX-A products and the single BTX-B product are approved for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain. OnabotulinumtoxinA is approved for treatment of blepharospasm and strabismus associated with dystonia; and incobotulinumtoxinA is approved for blepharospasm in patients who have previously been treated with onabotulinumtoxinA. BTX-A has also been found to be safe and effective for the management of focal dystonias. These botulinum toxin agents are not equivalent in dosing units, so caution must be observed when switching brands.

Patients selected to receive BTX for dystonia should meet three criteria:

- The dystonia should interfere with their functioning, comfort, or care to the degree that causes impairment and affects activities of daily living;
- Focal weakening following administration of the drug should not decrease their level of function; and
- The patient should understand that use of BTX may not completely address positioning, posturing, or secondary deformities.

Contraindications include pregnancy, lactation, comorbid neuromuscular disease (eg, amyotrophic lateral sclerosis or myasthenia gravis), and use of an aminoglycoside.

The need for BTX therapy should be reevaluated prior to each treatment; clinical benefit lasts 3 months or more. Electromyography may facilitate the location of target muscles, particularly since involved musculature may not be palpable and is often not superficial. In-office tools that help document baseline and posttreatment results, including videotaping dystonic limb movements and the use of rating scales, can be important for evaluating the patient’s progress.

Relief for cervical dystonia

The treatment of choice for focal dystonias and focal aspects of generalized dystonia is BTX. Both BTX-A and BTX-B offer effective palliative treatments for cervical dystonia by improving neck position, reducing pain, and decreasing disability in sufferers. The BTX solution is injected directly into the dystonic muscle at several locations, temporarily weakening the overactive muscle. The BTX dose is approximately proportional to the size of the muscle, although smaller muscles typically responsible for precision movement may require a relatively larger dose (Table 2). Doses may be modified according to clinical factors such as muscle bulk and severity of dystonia (Table 3).

<table>
<thead>
<tr>
<th>Potential muscles involved</th>
<th>Starting dose (units)</th>
<th>Starting range (units)</th>
<th>Approximate number of injection sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternocleidomastoid</td>
<td>40</td>
<td>15–75</td>
<td>2</td>
</tr>
<tr>
<td>Scalene complex</td>
<td>30</td>
<td>15–50</td>
<td>3</td>
</tr>
<tr>
<td>Splenius capitis</td>
<td>60</td>
<td>15 or 30–100</td>
<td>4</td>
</tr>
<tr>
<td>Splenius cervicalis</td>
<td>30</td>
<td>20–60</td>
<td>2</td>
</tr>
<tr>
<td>Semispinalis capitis</td>
<td>60</td>
<td>30–100</td>
<td>4</td>
</tr>
<tr>
<td>Longissimus capitis</td>
<td>60</td>
<td>30–100</td>
<td>4</td>
</tr>
<tr>
<td>Trapezius</td>
<td>40</td>
<td>20 or 55–100</td>
<td>3</td>
</tr>
<tr>
<td>Levator scapulae</td>
<td>40</td>
<td>20–100</td>
<td>3</td>
</tr>
</tbody>
</table>

*In this example, the botulinum toxin-A is onabotulinumtoxinA.
CHEMODENERVATION IN DYSTONIA

Relief following BTX injection for cervical dystonia occurs about 1 week later, with the greatest effect seen at about 2 to 6 weeks following injection; relief may last 12 to 16 weeks. Reinjections are not normally administered prior to 12 weeks’ duration in order to reduce the possibility of antibody formation. Concomitant interventions addressing depression and anxiety may have a significant effect on overall quality of life. Patients may also try several sensory tricks, called gestes antagonists, which may temporarily reduce or alleviate the dystonia. However, these tactile procedures—such as placing a hand on top of the head—lose their effectiveness over time.

Treatment of blepharospasm, focal limb dystonia
The use of BTX-A for blepharospasm is a significant improvement over the former clinical reliance on various oral medications, which, with the exception of baclofen, proved largely ineffective. Surgical treatments result in damage to muscular and nervous tissues, and so are reserved only for nonresponders to BTX-A therapy. BTX-A can provide effective relief and is the treatment of choice for focal limb dystonias. Goals of treatment include functional improvement, correction of abnormal posture, and relief from discomfort. Although a variety of oral medications may also be prescribed, drug toxicity and adverse effects can outweigh the benefit and are usually only used in cases of severe dystonia. Oral medications used for limb dystonia include anticholinergics, dopamine agonists and antagonists, baclofen, clonazepam or other benzodiazepines, and muscle relaxants.

Antibodies may bind to the drug in a small percentage of patients who regularly receive injections of BTX, rendering additional injections of that specific serotype of BTX ineffective. This immunoresistance can be avoided if clinicians inject only the smallest quantity of BTX that achieves clinical efficacy, avoid administering booster injections before the end of the minimum 12-week lockout period, and extend the period between treatments as long as possible. If immunoresistance does occur, the BTX should be exchanged for a different serotype.

Testing for nonresponse
Patients are said to be nonresponders to BTX therapy if at 4 to 6 weeks following injection they show no reduction in muscle tone. A functional test for nonresponse is to inject a small amount of BTX into either the frontalis or sternocleidomastoid muscle prior to starting treatment; asymmetric weakness demonstrates a response, indicating that either injection technique or muscle selection is the problem. In addition to the development of neutralizing antibodies, other possible reasons for nonresponse include a dose that is too low or an alteration in the pattern of muscles involved in the dystonic movement.

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Comprehensive treatment of Huntington disease and other choreic disorders

ABSTRACT

The management of choreic disorders presents significant challenges, including identifying the etiology of the disorder, treating and preventing motor symptoms, and managing a range of other neurologic and behavioral complications. Chorea may occur in several neurodegenerative, genetic, or drug-related conditions, and a thorough diagnostic evaluation is needed to identify the specific underlying causes. Some choreic disorders have specific treatable underlying etiologies, such as vitamin B₁₂ deficiency or drug-induced dyskinesia. Autoimmune disorders such as Sydenham chorea may be treated with penicillin, corticosteroids, intravenous immunoglobulin, or plasma exchange. Heredodegenerative choreas such as Huntington disease often respond to treatment with tetrabenazine or amantadine. Many other agents may be used nonspecifically for symptom control, including benzodiazepines, neuroleptics, and antiepileptic medications. In addition to motor symptoms, patients with Huntington disease or other choreic disorders often experience increasing depression, bradykinesia, cognitive impairment, aggressive behaviors, and other complications as the disease progresses. Caring for the caregiver is also a significant concern in the long-term treatment of choreic disorders.

Chorea is characterized by continuous, random, brief, involuntary muscle contractions that result from a variety of causes. These involuntary movements are nonstereotyped and irregular. Although choreic disorders are among the most common involuntary movement disorders, their diagnosis and treatment present several important challenges, including identifying and removing the cause if possible, controlling and preventing motor symptoms, and managing neuropsychologic complications. This article provides an overview of the diagnosis and treatment of choreic disorders, using Sydenham chorea to illustrate the management of autoimmune choreas and Huntington disease as the model for the management of heritable choreas.

Management of choreic disorders begins with a first-pass diagnosis and the use of symptomatic therapies. Even if this first pass yields no firm diagnosis, it at least rules out causes that have the most practical significance. A subsequent second-pass evaluation can be undertaken to look for rarer causes. Symptomatic therapies are continued throughout the diagnostic period. More specific therapies can be administered if an etiologic or pathogenic mechanism is determined (eg, postinfectious, autoimmune, metabolic).

CHOREIC DISORDERS: A PRACTICAL DIAGNOSTIC APPROACH

In general, choreic disorders may be subdivided into six categories:

1. Heredodegenerative disorders, such as Huntington disease and other genetically heterogeneous choreas, include Huntington disease–like 2 (HDL2) and benign hereditary chorea. Sporadic cases include those of unknown paternity; X-linked disorders (eg, McLeod syndrome); and autosomal-recessive disorders such as chorea-acanthocytosis, which is characterized by chorea, dystonia with prominent orofacial involvement, self-mutilation, myopathy, and neuropathy.

2. Drug-induced choreas include neuroleptic-induced tardive dyskinesia and nontardive hyperkinetic drug-related choreas, the most common of which is levodopa-induced dyskinesias. Tardive drug-induced choreas may occur while using the culprit drug, while tapering the drug, or after it has been discontinued. The culprit drugs are represented by dopamine-receptor blockers and include the first-generation neuroleptics (eg, phenothiazines, haloperidol), antidepressants (loxapine), and gastrointestinal agents (metoclopramide, prochlorperazine). Drug-induced choreas are possible with a wide range of pharmacologic agents, includ-
gang antiparkinsonian drugs (eg, levodopa, dopamine agonists, anticholinergics), sympathomimetics (eg, amphetamines, cocaine), anticonvulsants, calcium channel blockers, and oral contraceptives.1

3. Autoimmune choreas include Sydenham chorea, systemic lupus erythematosus, and antiphospholipid antibody syndromes. The latter encompass lupus anticoagulant and antiphospholip antibodies.

4. Metabolic choreas are most often associated with hyperthyroidism, although case reports have described choreas in patients with vitamin B12 deficiency. A variety of hereditary metabolic diseases are also included in this category.

5. Vascular choreas include polycythemia vera and cerebrovascular accidents, the latter frequently presenting as hemiballismus. Polycythemia vera is associated with a high incidence of neurologic symptoms, including a reported incidence of chorea of 0.5% to 5%,4 and should be considered as a potential cause of chorea.

6. Other choreic disorders include a variety of entities such as rare paraneoplastic disorder/syndrome, and posttraumatic and postanoxic presentations.

The first-pass diagnostic approach includes a family history, drug history, and brain magnetic resonance imaging to identify potential structural causes of chorea. Genetic testing for Huntington disease or other choreic disorders may also be performed, although it is essential to consider the potential implications of a positive test result. Intensive pretest and posttest counseling is important both for the patient and for currently asymptomatic family members who may also be affected.5

Other testing includes:
- Complete blood count
- Creatine phosphokinase
- Peripheral smear for acanthocytes
- Comprehensive metabolic panel
- Ceruloplasmin level
- Measurement of thyroxine (T4) and triiodothyronine (T3)
- B12 tests
- Antinuclear antibody sedimentation rate
- Lupus anticoagulant-antiphospholip antibodies
- Antistreptolysin O (ASO) titer
- Anti-DNase-B titer.

General Considerations for the Treatment of Choreic Disorders

In some cases, choreic disorders have a treatable underlying etiology, such as thyroid disease or vitamin B12 deficiency. Tardive syndromes may require treatment beyond drug discontinuation, including use of dopamine depletors for the classic tardive dyskinetic syndromes and anticholinergics for the tardive dystonic syndromes. Levodopa dyskinesia may be treated using amantadine, clozapine, or deep brain stimulation.6 The treatment of patients with autoimmune choreas is not well defined. It may include anticoagulation in patients with positive antiphospholip antibodies to prevent venous or arterial thromboembolism,7 but the risk of arterial thromboembolism is uncertain, and it is unclear whether chorea is truly a harbinger of vascular events.

A negative ASO titer does not exclude Sydenham chorea, a result of childhood infection with group-A beta-hemolytic streptococcus, and antibiotics should be considered in the appropriate context. Some researchers have argued that immune responses associated with acute infections may result in autoimmune neuropsychiatric symptoms. In pediatric patients, this has been referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).8

A related phenomenon has been proposed as a potential mechanism of some types of chorea, although the relationship between acute infection and chorea is controversial. Patients with elevated ASO titer or anti-DNase-B titers may be candidates for antibiotics. By 6 weeks after the onset of infection, these titers will fall and a diagnosis of Sydenham chorea can be postulated or based exclusively on clinical judgment.

Sydenham Chorea

Unique to Sydenham chorea is the use of penicillin as prophylaxis. Other than that, the management of Sydenham chorea exemplifies the management approach for the larger category of autoimmune choreic disorders. Pathogenic-based treatment options include immune modulation with corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange; all treatments must be administered in the appropriate clinical context.

One double-blind clinical trial examined the effectiveness of corticosteroid treatment in children with Sydenham chorea randomly assigned to receive either prednisone (n = 22) or placebo (n = 15).9 Prednisone was administered at a dose of 2 mg/kg/day for 4 weeks, followed by gradual tapering and discontinuation. The median time to remission of chorea was significantly lower for patients in the prednisone group (54.3 days) compared with those in the placebo group (119.9 days; P < .001). Patients in the prednisone group also exhibited significantly better scores on a chorea intensity rating scale at 8 weeks and 12 weeks (P < .001). Potential limitations of this approach include relapse of chorea symptoms and corticosteroid-related adverse events (eg, Cushing syndrome, hypertension).

A second study compared the effectiveness of three modalities: IVIG at a dose of 1 g/kg/day for 2 days (n = 4), plasma exchange (n = 8), and prednisone (n = 6).10 Although differences between treatment groups
were not statistically significant, the authors noted that the clinical improvement in chorea symptoms tended to be greater for patients who received IVIG or plasma exchange than for those who received prednisone. Mean chorea scores improved from baseline by 72% for the IVIG group, 50% for the plasma exchange group, and 29% for the prednisone group.

After etiology-dependent treatments have been considered, several other options may be effective regardless of the specific etiology. These include symptomatic treatments such as haloperidol, atypical neuroleptics, and amantadine. Antiepileptic medications or benzodiazepines may also help to control symptoms, although less information is available about the use of these agents for the treatment of Sydenham chorea. Tetrabenazine may be considered for patients who will require long-term treatment.

**HUNTINGTON DISEASE**

Pharmacotherapy of Huntington disease may be unnecessary if symptoms are mild or not bothersome. Symptomatic treatment options include tetrabenazine, amantadine, and either first-generation neuroleptics (eg, haloperidol) or second-generation atypical neuroleptics (eg, olanzapine, quetiapine, risperidone, ziprasidone).

**Treating choras with tetrabenazine or amantadine**

Considerable recent attention has focused on the efficacy and safety of tetrabenazine for the treatment of Huntington disease and other choreic disorders. Tetrabenazine is a central monoamine depleter that reversibly binds to the type-2 vesicular monoamine transporter. The TETRA-HD study examined the efficacy and safety of tetrabenazine for the short- and long-term control of Huntington disease. An initial study compared tetrabenazine with placebo in 75 patients who were treated for up to 13 weeks. In an extension study, all patients received individualized tetrabenazine doses for up to 80 weeks.

The mean total maximal chorea (TMC) scores from the Unified Huntington Disease Rating Scale (UHDRS) decreased markedly during the first 10 weeks of tetrabenazine treatment, remained lower than baseline throughout 80 weeks, and then returned to baseline levels after tetrabenazine discontinuation (Figure 1). At week 80, the mean TMC score was reduced by 4.6 UHDRS units compared with baseline ($P < .001$). The long-term extension phase was completed by 45 of 75 patients. Treatment-related adverse events that prompted discontinuation included depression, delusions, and vocal tics. The most commonly reported adverse events included sedation or somnolence ($n = 18$), depressed mood ($n = 17$), anxiety ($n = 13$), insomnia ($n = 10$), and akathisia ($n = 9$). Scores of parkinsonism and dysphagia increased significantly from baseline over the 80-week study.

Amantadine is an option for patients who cannot tolerate tetrabenazine. A double-blind, placebo-controlled study performed by researchers at the National Institutes of Health (NIH) examined the efficacy and safety of amantadine in 24 patients with Huntington disease. Patients were treated with oral amantadine 400 mg/day or placebo for 2 weeks, and were then crossed over to the other treatment. Amantadine was associated with a median reduction in extremity chorea score at rest of 36% from baseline ($P = .04$), versus 0% improvement with placebo. The mean improvement with amantadine was 56% for the 10 patients with the highest drug plasma levels.

Improvement in chorea scores from baseline for amantadine compared with placebo was rated with four different methods: (1) maximal chorea severity measured from video recordings; (2) maximal chorea severity measured by live raters; (3) chorea severity at rest measured from video recordings; and (4) extremity chorea at rest measured from video recordings. Amantadine was superior to placebo according to all four rating methods. Treatment was generally safe and well tolerated, and no consistent changes in cognitive function were noted with amantadine therapy.

A second study examined the effects of amantadine as a 2-hour IV infusion in nine patients with Huntington disease. Amantadine or placebo was administered in a randomized, double-blind manner on the first day of the study, and patients were then crossed over to the other treatment on the second day. All patients then received open-label oral amantadine for an additional 1 year. During the randomized placebo-controlled phase, mean dyskinesia scores, evaluated using the Abnormal Invol-
untary Movement Scale, were significantly lower for patients randomly assigned to amantadine compared with placebo. During the randomized placebo-controlled phase, the decrease in mean dyskinesia score was significantly greater 90 minutes after treatment with amantadine compared with placebo (Figure 2). In the open-label amantadine continuation phase, oral amantadine was associated with a further gradual improvement in symptoms over 3 to 6 months. No significant changes were observed in neuropsychologic tests or psychiatric rating scales.

Managing nonmotor complications
In addition to addressing chorea, it is also important to manage nonmotor complications of Huntington disease, including cognition, mood, and thought disorders. Rivastigmine was assessed for the treatment of motor symptoms, functional disability, and cognitive impairment associated with Huntington disease in an open-label study of 18 patients; 11 received rivastigmine 6 mg/day and 7 control patients did not. Motor and cognitive function were assessed for up to 2 years by raters who were blinded to treatment assignment. Ratings on a global motor performance scale were significantly better for patients who received rivastigmine than for control subjects. Rivastigmine treatment was also associated with trends toward improvements in functional disability and cognitive impairment, although these differences were not statistically significant.

A small open-label study examined the effects of donepezil for movement and cognitive symptoms associated with Huntington disease. Donepezil did not significantly improve cognitive symptoms, although the study enrolled only eight patients. All patients tolerated oral donepezil at a dose of 5 mg/day, but four patients withdrew from the study when the dose was increased to 10 mg/day. In two patients, chorea worsened and falls increased, moderate to severe diarrhea developed in three patients, and one patient reported anxiety and irritability.

Depression is another common complication of Huntington disease. The incidence of depression among patients with Huntington disease is approximately 40%, and the risk of suicide is at least eightfold greater than that among the general population. Treatment must be guided by clinical judgment. Selective serotonin reuptake inhibitor antidepressants have been recommended. Other options to manage depression include mirtazapine, monoamine oxidase inhibitors, or electroshock therapy. Mood-stabilizing agents (eg, carbamazepine, lamotrigine, valproate) may also be indicated in helping with impulse control. Haloperidol and second-generation antipsychotics are used for the treatment of a broad range of psychiatric conditions, many of which may overlap with Huntington disease, including schizophrenia and schizophasic disorder, schizoaffective disorder, bipolar disorder, dementia, and disruptive behavior. The risk of tardive dyskinesia may be as much as fivefold lower with second-generation antipsychotics. Many patients with Huntington disease require treatment for aggression. A
variety of approaches are available, including behavior modification, the antidepressant sertraline, buspirone, antipsychotic agents (eg, risperidone, olanzapine), propranolol, and lithium (combined with haloperidol).

Long-term care considerations
As a consequence of the diverse clinical manifestations of choreic disorders in movement, function, mood, and cognition, the treatment of Huntington disease requires a multidisciplinary approach that involves a number of different health care specialties across the long-term course of the disorder. Members of the Huntington disease treatment team may include neurologists, psychiatrists, nurses, social workers, geneticists, physical therapists, occupational therapists, speech therapists, dietitians, and other supporting groups or professional societies. The clinical manifestations of Huntington disease may evolve over time, as symptoms such as bradykinesia, dystonia, rigidity, cognitive decline, and gait instability become more significant. As a result, optimal management strategies for patients with Huntington disease may change significantly across the long-term course of the disease. During the early course of the disease, the typical clinical presentation is largely hyperkinesia, irritability, and distractibility. These patients will require initiation of drug therapy and linkage to sources of support. In the later stages of the disease, the presentation shifts to a more hypokinetic and apathetic profile, and patients are more likely to require drug regimen review and modification, nursing home placement, and palliative care services.

Another important concern in Huntington disease treatment is care of the caregiver. Surveys show that the key concerns of caregivers include the expertise of the health care professionals who are treating the patient and the availability of sufficient services in the community. Several resources are available for Huntington disease caregivers, including local support groups, the Huntington’s Disease Society of America, Q Foundation, and the Huntington Study Group. The Lundbeck pharmaceutical company operates a patient assistance program (LundbeckShare.com) as well as an information center that can be accessed toll free at (888)457-4273. Approximately 90% of patients who request copayment assistance qualify for aid, regardless of the type of insurance they carry.

■ SUMMARY AND CONCLUSIONS
The approach to a patient with chorea starts with a search for specifically treatable etiologies. Autoimmune, metabolic, and vascular causes should be sought first and treated. The symptomatic treatment of all choreas is based on the model described here for Huntington disease, and includes attention to cognitive, psychiatric, and social support issues. The recommended approach is multidisciplinary, with a change in the mix of services as the disease progresses. It is also important to recognize the burden of Huntington disease on the caregiver and consider steps to make this burden more manageable.

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Tourette syndrome (TS) is a disorder characterized by childhood onset multiple motor and vocal tics often accompanied by features of obsessive compulsive disorder, attention deficit hyperactivity disorder (ADHD), or other behavioral manifestations. Tics may be simple or complex, and may include motor and vocal components. Abnormal function of the basal ganglia is thought to be an important underlying cause of tics and other movement disorders. Treatment of TS requires a thorough understanding of the phenomenology of the disease for the individual patient, and should focus on symptoms that are especially troubling. Some nonpharmacologic approaches may help to improve tic severity, including conditioning techniques, relaxation training, and hypnosis. Options for pharmacotherapy include dopamine blockers and depleters, benzodiazepines, central alpha-adrenergic blockers, and botulinum toxin. Many patients require therapy for comorbid conditions such as anxiety, depression, or ADHD. In case studies and small patient series, deep brain stimulation has been shown to markedly reduce tic severity and functional impairment associated with TS. While onset is most frequently in childhood, TS should not be considered exclusively a disorder of pediatric patients. The complications and comorbidities that are encountered in children and adolescents often persist into adulthood.

Tourette syndrome (TS) is part of a spectrum of tic disorders. Tics are sudden, rapid, stereotyped, repetitive, nonrhythmic movements or vocalizations affecting discrete muscle groups, and are preceded by a sensory component. Patients in whom tic suppression is attempted report the experience of a sensation of inner pressure that must be released. This eventually results in the performance of motor movement or vocal sounds. TS is a disorder of childhood onset that is characterized by multiple motor and vocal tics. In some cases, there are features of obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), or other behavioral manifestations such as coprolalia, echopraxia, palilalia, and self-injury.1,2 The spectrum of tic disorders includes:

- Transient tics of childhood (tic duration less than 12 months)
- Chronic motor or vocal tics (lasting more than 12 months), and
- TS (variable motor and vocal tics lasting more than 12 months).

Many children meet the diagnostic criteria for TS between the ages of 6 and 9 years, but symptoms may improve by adulthood. The eventual loss of tics over time reflects the maturation of brain systems that control ballistic action.3

The tics that accompany TS may be defined as simple or complex, and as motor or vocal. Simple motor tics involve only a few muscles, such as eye blinking, shoulder shrugging, or facial grimacing. Complex motor tics involve multiple groups of muscles that are recruited in orchestrated bouts (eg, hand gestures, jumping, touching, or pressing), and may include copropraxia (a sudden tic-like vulgar, sexual, or obscene gesture) or echopraxia (involuntary, spontaneous imitation of someone else’s movements). Simple vocal tics are meaningless sounds such as throat clearing, grunting, sniffing, snorting, and chirping. Complex vocal tics involve speech and language such as sudden, spontaneous expression of single words or phrases, or speech blocking.4

Tics may be acquired as a consequence of other disorders, including head trauma, encephalitis, stroke, carbon monoxide poisoning, Creutzfeldt-Jakob disease, neurosyphilis, hypoglycemia, or Sydenham chorea.5 Genetic disorders such as Huntington disease may be associated with tics. Tics may also occur with certain chromosomal abnormalities or be associated with some neuropsychiatric disorders. Finally, tics may be
TICS AND TOURETTE SYNDROME

caused by a large number of medications or illicit drugs, including cocaine, amphetamines, antipsychotics, and antidepressants.

The prevalence of all types of tics in childhood is approximately 6% to 12%, although the prevalence of chronic vocal tics is approximately 1 to 10 per 1,000 children and adolescents.6 TS is especially common among autistic children and in those with Asperger syndrome and other autistic spectrum disorders. A survey of patients at Cleveland Clinic Florida found that tics and TS accounted for 8% of all patients with movement disorders. Of patients with tics or TS who were older than 18 years, 70% were male.

PATHOPHYSIOLOGY OF TOURETTE SYNDROME: ROLE OF THE BASAL GANGLIA

Although the pathophysiology of TS is not completely understood, abnormal function of the basal ganglia is thought to be a central component of the disorder. The basal ganglia normally act to facilitate voluntary movements while suppressing competing involuntary ones. Abnormalities of basal ganglia activity are important in several disorders of motor function.7 Output neurons from the basal ganglia inhibit thalamic motor nuclei and midbrain neurons of the extrapyramidal motor system, and act to inhibit motor pattern generators in the cerebral cortex and brainstem. Hyperkinetic disorders, including tics, chorea, and dystonia, are thought to result at least in part from impaired inhibition of unwanted motor activity from the basal ganglia to downstream motor centers.7

Family heritability studies provide strong support that TS is a genetic disorder. For example, the concordance rate is 86% for monozygotic twins versus 20% for dizygotic twins.8 Chromosomes linked to TS include 2p32.2 and 13q31.1.9,10 Interactions between genetics and environment are also thought to play a significant role. The concept of pediatric autoimmune neuropsychiatric disorders associated with streptococcal (PANDAS) infections has been proposed to explain an apparent temporal association between streptococcal infections and exacerbation of tics. According to this model, molecular mimicry between streptococcal antigens and endogenous brain antigens results in an autoimmune attack.11 However, the identification of specific antibodies against basal ganglia cells remains controversial.12

MANAGEMENT OVERVIEW

Accurate diagnosis of TS is essential, and includes a complete history and neurologic examination. The tic phenomenology (complex vs simple) should be characterized, and the patient should be carefully questioned to identify the symptoms that are most bothersome (eg, motor or vocal tics, OCD, or ADHD). Pharmacotherapy should be reserved for problems that are functionally disabling and not remediable by nonpharmacologic interventions.

Treatment may also be required for other neuropsychiatric symptoms. Anxiety and depression have been reported in 19% to 80% of patients with tics, and depression is strongly correlated with the duration and severity of tics.13,14 Episodic outburst (rage), self-injurious, OCD, antisocial, and oppositional behaviors are all more common among individuals with tic disorders.15 Personality disorders may be related to OCD, ADHD, or to family or economic issues. Tic disorders are also associated with an increased incidence of somatic complaints, as well as higher rates of academic difficulties, which may be related to ADHD or medications. Sleep disturbances affect an estimated 20% to 50% of patients, and may include difficulty initiating or maintaining sleep, restlesslessness, movement-related arousal, or parasomnia.16

Education is an important part of treatment, and may include the patient, family members, teachers or other school staff, and work colleagues. A number of behavioral or psychosocial approaches may help to improve tics, including conditioning techniques, relaxation training, biofeedback, habit reversal, awareness training, and hypnosis.17

PHARMACOLOGIC TREATMENT: THREE TIERS

Options for the pharmacologic treatment of tics and TS include dopamine blockers, dopamine depleters, benzodiazepines, central alpha-adrenergic blockers, and botulinum toxin. Pharmacotherapy options can be divided into three tiers (Table), with first-tier drugs considered first-choice treatments.

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First-tier therapies
The alpha-adrenergic blockers clonidine and guanfacine are first-tier therapies. Treatment should be initiated at a low dose and escalated gradually according to response, which is determined by the severity, and not the presence, of tics. Clonidine may be administered at a dose of 0.025 mg two or three times daily or, for maintenance, 0.1 mg three times daily; another option is 0.1, 0.2, or 0.3 mg weekly by transdermal administration. Guanfacine may be administered at a dose of 1 mg once daily. Alpha-adrenergic blockers are useful for the treatment of mild tics, and are considered first-line therapy for tic suppression. Side effects may include dry mouth, somnolence, and, rarely, blood pressure fluctuations.

Agents that affect gamma-aminobutyric acid (GABA) neurotransmission have been associated with improved symptoms of tic disorders. For example, both clonazepam and diazepam have been reported to reduce TS symptoms. Both of these benzodiazepines are associated with sedation, blunting of cognition, and exacerbation of depression, however.

Second-tier therapies
Second-tier therapies, consisting of neuroleptics, induce a rapid treatment response. Haloperidol may be started at a dose of 0.25 mg once daily, with a maintenance dosage of 0.5 to 3.0 mg/day. Cognitive blunting or extrapyramidal side effects are rare in patients with TS, but the potential for these side effects should be thoroughly discussed with the patient or parent/guardian before treatment. Pimozide 0.5 mg (2 to 6 mg/day for maintenance) may be associated with tremor or parkinsonian symptoms (predominantly akinesia). Risperidone 0.25 mg/day (0.5 to 4 mg/day for maintenance), olanzapine 2.5 mg/day (5 to 10 mg/day for maintenance), and quetiapine 25 mg twice daily (100 to 300 mg/day for maintenance) are associated with potential adverse effects of extrapyramidal symptoms, weight gain, and diabetes.

Third-tier therapies
Dopamine agonists (reserpine and tetrabenazine) and botulinum toxin are third-tier therapies. Reserpine, although rarely used in current clinical practice, may be administered at doses of 0.1 to 0.25 mg/day, titrating upward on the basis of clinical response. Tetrabenazine may be administered at a starting dose of 12.5 mg/day, with higher doses as needed depending on the response to treatment. Adverse effects include hypotension, sedation, extrapyramidal symptoms (predominantly parkinsonism), and depression.

The exact mechanism by which tetrabenazine produces this suppression effect is unknown, but it is believed to be related to its effect of reversibly depleting monoamines. At least three neuronal protein classes regulate the effects of dopamine on voluntary and involuntary movement. The two presynaptic proteins are vesicular monoamine transporter subtype 2 (VMAT2) and dopamine transporter (DAT). Postsynaptically, dopamine activity is regulated by G-protein–linked dopamine receptors (eg, the D2 receptor). Tetrabenazine reduces the uptake of monoamines (including dopamine) into synaptic vesicles by reversibly binding to VMAT2, resulting in degradation of dopamine within axon terminals by monoamine oxidases. By blocking dopamine transport, tetrabenazine depletes dopamine with greater selectivity than it does other monoamines.

The dosage of tetrabenazine for the treatment of motor disorders, particularly chorea, was established in the Huntington Study Group (HSG) clinical trial. In the HSG trial, a starting dose of 12.5 mg on day 1 was increased to 12.5 mg twice daily on days 2 to 7, and then by 12.5 mg/day at weekly intervals until the desired clinical effect, intolerable adverse effects, or a maximum dose of 100 mg/day was reached. Daily dosages of 37.5 mg or more are administered in three divided doses. Adverse events (reported in 70% of patients who received placebo and 91% of patients who received tetrabenazine) include sedation or somnolence, insomnia, and fatigue. These findings may be carried over to patients with tics.

Botulinum toxin may also help to control tics—especially dystonic tics. The premonitory symptoms of TS are usually unaffected by botulinum toxin. The adverse effect profile for patients with TS is similar to that of patients with dystonia or facial dyskinesia, and may include soreness, transient weakness, ptosis (if injected for eye blinking), and mild transient dysphagia (if injected into the larynx).

MANAGING COMORBID CONDITIONS
Approximately 30% of patients with TS also have OCD. Treatment options include selective serotonin reuptake inhibitors at standard doses, and the tricyclic antidepressant clomipramine (25 mg once or twice daily, or 75 mg/day in sustained-release form). Trazodone, a serotonin antagonist and reuptake inhibitor that is associated with a lower incidence of anticholinergic effects, may be initiated at a dose of 50 mg/day and slowly increased to 150 to 400 mg/day depending on clinical response.

As many as 60% of patients with TS may also have ADHD. Methylphenidate is helpful for the treatment of ADHD and does not exacerbate tics, but it is a restricted medication. The recommended dose is 20 mg once daily, titrated upward as needed based on response.Atomoxetine carries a warning regarding increased risk of suicide. It has also been associated with an increased risk of sexual dysfunction and behavioral changes, including aggressive behaviors, agitation, and irritability.
Deep brain stimulation (DBS) has been shown to improve TS in single-case studies and in small series, although the long-term benefit is unclear. Potential targets of stimulation include midline thalamic centromedian-parafascicular (CM-PF) nuclei, the ventralis oralis complex of the thalamus, motor and limbic globus pallidus pars interna (GPI), and the anterior limb of the internal capsule. In particular, stimulation of the sensorimotor GPI may ameliorate hyperkinetic states.

One report described the results of DBS implantation in a 15-year-old boy with TS who had not responded to several pharmacologic treatment options. Six months after implantation, the patient exhibited markedly improved tic severity as measured using the Yale Global Tic Severity Scale, including a 76% reduction in motor tic severity, 68% reduction in vocal tics, and a complete resolution of impairment.

Published consensus criteria for the selection of suitable candidates for DBS include age greater than 25 years, chronic and severe tics with severe functional impairment for at least 12 months, tics that are frequent and noticeable in most situations most of the time, failure of conventional medical therapy, medical stability for 6 months, and willingness to participate in ongoing psychologic interventions. Exclusion criteria include the presence of another medical condition that could explain the tics, an unstable medical condition, being considered likely to benefit from psychologic interventions, psychosocial factors that may complicate the recovery process or make it difficult to assess outcome, and unwillingness to participate in ongoing treatment for psychosocial problems or risk factors. Other factors that should be considered include comorbidities, the variability in tic severity over time, the involvement of a multidisciplinary treatment team, results of a thorough neuropsychologic assessment, expertise of the surgical team, and access to imaging facilities for presurgical mapping and postsurgical evaluation.

**SUMMARY AND CONCLUSIONS**

Tourette syndrome is not uncommon among the adult population of a typical neurology practice, and should not be considered exclusively a pediatric diagnosis. Several treatment options are available, including behavioral approaches and several medications. Treatment should focus on the most disabling symptoms. Neuropsychologic assessment and psychologic support may be necessary for some patients. The same comorbidities that are encountered in children are usually evident in adult patients as well. In medically refractory cases, DBS surgery may be helpful.

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Surgical considerations for tremor and dystonia

ABSTRACT

Deep brain stimulation (DBS) is among the most effective approaches for the treatment of patients with advanced movement disorders. In patients with essential tremor, stimulation typically targets the ventral intermediate nucleus of the thalamus. Results of several studies have shown that over a follow-up period of 1 to 5 years, the severity of tremor decreases by an average of approximately 50% from baseline. Ongoing research continues to define the optimal stimulation parameters for patients with tremor, including frequency, voltage, and pulse width. In patients with dystonia, DBS typically targets the globus pallidus internus or the subthalamic nucleus. Long-term prospective clinical trials demonstrated reductions in motor severity rating scale scores of approximately 50% to 80% over follow-up periods of 2 to 3 years. Serious adverse events were uncommon, and included lead failures and infections. Appropriate candidates for DBS treatment of dystonia include patients with an unequivocal diagnosis of dystonia and significant disability. Several issues in the use of DBS for movement disorders remain unresolved, including the intensity of appropriate medical management before undergoing DBS, the importance of intraoperative mapping, optimal stimulator programming, and the time course of the beneficial effects of treatment.

Over the last decade, several studies have demonstrated that deep brain stimulation (DBS) is among the most effective approaches for the treatment of patients with advanced movement disorders, including chorea, levodopa-induced dyskinesia, tremor, and dystonia.1 The goal of DBS is to restore function or relieve pain by stimulating neuronal activity through surgically implanted electrodes. DBS produces marked and persistent reductions in abnormal movements in patients with common hyperkinetic disorders, with a generally low incidence of serious adverse events in pediatric patients and adults.

DEEP BRAIN STIMULATION FOR ESSENTIAL TREMOR

Tremor is a rhythmic, involuntary, oscillatory movement of a body part. Tremors may be subdivided into several categories on the basis of clinical signs and symptoms, including rest, postural, and kinetic.2 Essential tremor is the most common tremor disorder, affecting an estimated 5% of the population over the age of 60 years.3 Tremor is also commonly associated with other neurologic conditions, including multiple sclerosis, Parkinson disease, and severe head trauma.3 Hand, head, and vocal tremor are the most common clinical manifestations of essential tremor, and may significantly interfere with normal function.4 For example, the effect of essential tremor on a simple hand-drawing task is illustrated in Figure 1, which demonstrates the marked tremor-related impairment in a patient's ability to draw a spiral shape and the resulting improvement in hand coordination after the application of DBS.

Improvement with thalamic DBS

The ventral intermediate nucleus (VIM) of the thalamus is the most common target for DBS treatment of essential tremor. Several studies have demonstrated significant long-term improvement in tremor following thalamic DBS.1 Most studies enrolled 20 to 30 patients, who were followed for 1 to 5 years after device implantation. On average, these studies reported an improvement in overall tremor of approximately 50% from baseline with thalamic DBS.

Patient selection and stimulation parameters

Both authors reported that they have no financial interests or relationships that pose a potential conflict of interest with this article. This article is based on Dr. Cooper’s presentation at “The Annual Therapy Symposium on Movement Disorders for the Modern Clinician” held in Fort Lauderdale, Florida, on January 29, 2011. The article was drafted by Cleveland Clinic Journal of Medicine staff, including Mark Bowes, PhD, and was then reviewed, revised, and approved by Dr. Cooper. doi:10.3949/ccjm.79.s2a.08

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patient characteristics should be considered, including age, comorbid conditions, surgical risk, patient preference, social and employment factors, and social support. Research is ongoing to define the stimulation parameters that are most important for ensuring symptom control in patients undergoing DBS for tremor. Studies that have modeled tremor response to DBS across a range of stimulation parameters have found that suppression of tremor is most closely associated with stimulation voltage and frequency, with pulse width producing less of an effect. Figure 2 shows tremor power (measured in decibel units) associated with different combinations of frequency and pulse width applied to the VIM in nine patients with essential tremor. The observations from this study suggest that stimulation programming is complex even for essential tremor, a condition for which programming is generally among the simplest to perform.

DEEP BRAIN STIMULATION FOR DYSTONIA

Dystonia is characterized by involuntary twisting muscle contractions causing abnormal postures sometimes accompanied by jerky or repetitive involuntary movements. It may be classified according to the body part affected as generalized, segmental, or focal; in some cases it may be classified as multifocal dystonia or hemidystonia. Dystonia is also classified as primary or secondary, according to etiology. Primary dystonias are those not caused by any other identifiable condition and not associated with other neurologic abnormalities. These include idiopathic and some genetic dystonias, such as the DYT1 torsinA gene mutation. DBS of the globus pallidus internus (GPI) or subthalamic nucleus (STN) was approved by the US Food and Drug Administration under a humanitarian device exemption in 2003 for the treatment of primary generalized dystonia (PGD) in patients aged 7 years and older; GPI is the more common target.

Evidence of efficacy

Several clinical studies have demonstrated the efficacy of DBS for patients with disabling PGD that is unresponsive to pharmacotherapy.

Long-term efficacy. Isaías and colleagues examined long-term safety and efficacy of DBS in 30 consecutive patients with PGD who were followed for at least 3 years after pallidal DBS surgery. DBS was delivered bilaterally in 28 patients and unilaterally in 2 patients. Clinical rating scales of motor function improved by a mean of 82.5% after 2 years, and dystonia-related disability improved by a mean of 75.2%. Improvement in motor function from baseline was noted for all 30 subjects. In five patients who were followed for 7 years, improvement in motor function remained greater than 80% at the last follow-up visit. Transient regressions were noted for patients with hardware failures or whose batteries had reached the end of life. Stimulation-related adverse events were reported for three patients and included speech difficulties and, in one patient, transient blepharospasm.

Vidailhet and colleagues examined the efficacy of bilateral pallidal stimulation in 22 patients with PGD who were followed prospectively for 3 years. Mean improvement from baseline in motor function on a dystonia rating scale was 51% after 1 year and 58% after 3 years (P = .03). Significant improvement was noted for individual ratings of upper and lower limb function scores. Health-related quality of life was also significantly improved at 3-year follow-up (P = .05). Serious adverse events were reported for three patients, including two lead fractures and one infection.

Results from double-blind trial. Kupsch and colleagues performed a randomized, double-blind clinical trial comparing pallidal DBS versus device implantation and sham stimulation in 40 patients with primary segmental or generalized dystonia. After 3 months, the mean change from baseline in severity of dystonia was 15.8% for patients who received DBS versus 1.4% with sham stimulation (P < .001). At the conclusion of the double-blind treatment phase, patients entered an open-label extension phase in which all patients received DBS for another 3 months. The initial benefit of treatment was sustained across the entire 6-month study period for patients initially randomized to DBS, whereas patients who were initially randomized to sham stimulation exhibited improved motor function during the open-label extension phase. Ratings of disability and quality of life also improved for patients receiving
DBS at the end of the 6-month study. Adverse events included dysarthria (five patients), serious infections (four patients), and lead dislodgement (one patient).

**Response with DYTI mutation.** Coubes and colleagues examined the long-term efficacy and safety of bilateral DBS in 31 children and adults with PGD. PGD is associated with autosomal *DYTI* mutations in approximately 30% of cases, and these authors examined the effects of treatment in patients with and without the *DYTI* mutation. After 2 years of treatment, mean scores on a dystonia clinical rating scale decreased by 79% from baseline, and mean disability ratings decreased by 65%. The improvement in clinical dystonia rating scale scores was significantly greater for children than adults after 2 years (84.7% vs 70.1%; *P* = .04). In children, functional improvement was greater after 2 years in the subset of patients with *DYTI* mutations than in the subset of patients without (76.1% vs 44.5%; *P* = .03), whereas in adults, *DYTI* mutation status did not significantly influence response to treatment. One case of unilateral infection was noted, which required removal of the implant with successful reimplantation 6 months later. No other adverse events were reported.

**Patient selection**

Appropriate patients for DBS include those with an unequivocal diagnosis of dystonia and significant disability. Etiology and type of dystonia should also be considered. Patients with secondary dystonia (eg, due to structural brain lesions or heredodegenerative disorders) generally do not respond to DBS as well as patients with primary dystonias. A possible exception is tardive dystonia, which is caused by past exposure to dopamine receptor–blocking drugs. Although it is a secondary dystonia, tardive dystonia may respond well to DBS. Data on this point remain limited. Moreover, with tardive dystonia (as well as Sydenham chorea and poststroke hemiballismus), there may be spontaneous remission. DBS in these conditions should therefore be considered when enough time has elapsed that the likelihood of spontaneous remission is low.1

Not all dystonic symptoms have been shown to respond equally to DBS. Evidence of effectiveness is stronger and more consistent for limb and axial dystonia than for dystonic impairment of speech and swallowing. Phasic dystonia (jerky or rhythmic movements) appears to respond better than fixed postures. A critical point is that fixed postures not caused by electrically active muscle contraction will not respond to DBS. For example, bony deformity of the spine, joint disease, or tendon shortening cannot be expected to improve with DBS. The situation is complicated, since such conditions may develop as secondary consequences of dystonia. The potential for their development may warrant earlier rather than later DBS surgery in childhood-onset PGD.10

**UNRESOLVED ISSUES IN DBS FOR DYSTONIA**

**How aggressively should other therapies be tried before starting DBS?**

Pharmacologic options include a range of oral, intramuscular, and intrathecal agents. Injection of botulinum toxin to denervate affected muscles is a mainstay of treatment for focal or segmental dystonia, but often fails to improve symptoms because of the involvement of a large number of muscles, complexity of the movement pattern, or the development of neutralizing antibodies.8 With the exception of levodopa-responsive PGD, other

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**FIGURE 2.** The upper curve (labeled with lower-case letters) shows various combinations of pulse width (in microseconds) and pulse frequency for frequencies less than 90 Hz. The lower curve (labeled with upper-case letters) shows combinations of pulse width and frequency for frequencies of 90 Hz or greater. Each lettered point represents a frequency–pulse-width combination. Points fell into two clusters that were dependent on stimulation frequency but not pulse width. For low-frequency stimulation (upper curve), tremor increased with increasing voltage. At higher stimulation frequencies (lower curve), tremor was related to voltage in a U-shaped function. Tremor decreased as voltage increased to approximately 2 volts, and then worsened at higher voltages.5

pharmacologic therapy for PGD is generally of limited effectiveness for controlling symptoms of dystonia. Oral or intrathecal baclofen may improve symptoms, but often produces unacceptable sedation.

**How important is intraoperative microelectrophysiology?**

Although contemporary imaging techniques are important in the correct placement of stimulating electrodes, the available techniques do not always provide sufficient resolution to delineate the STN or GPi. The accuracy of electrode placement may also be influenced by distortions caused by lack of homogeneity among magnetic resonance images, brain shift, and signal deflections from cannulae or electrodes. These errors may result in significant deviation of electrode placement from the intended target. Microelectrode recording and microstimulation may be used to map the target region and refine the surgical target. It is widely, but not universally, held that this strategy contributes to superior accuracy and outcomes; it ordinarily requires an awake procedure, which is not always feasible in patients with severe dystonia or in pediatric patients.

**How should programming (stimulator adjustment) be performed?**

Research continues to refine our understanding of how electrical parameters such as voltage, frequency, and pulse width affect clinical outcomes in patients undergoing DBS for dystonia. Some programming approaches, such as long pulse width and high frequency, that were once generally accepted are now widely questioned. Another major unresolved question is: “How long should it take to see the results of stimulation?” In the clinical studies described above, continued improvement was generally observed over months or even years, and, in most patients, stimulators are incrementally adjusted over an extended period. However, some patients may experience much more rapid onset of benefit.

**Long-term DBS management of dystonia**

Unlike DBS for Parkinson disease or even essential tremor, DBS for dystonia is performed in young patients. This creates special challenges in pediatric patients, who can be expected to grow and develop after device implantation. As a result, children may require additional surgeries to reposition devices.

In addition, the most widely used devices require repeated battery replacement surgeries, although newer rechargeable devices are becoming available.

Finally, there is a nontrivial incidence of hardware-related complications when devices are used continuously for many years. Although individual dystonia patients vary in the acuity of their response to the cessation of stimulation, deterioration can be acute and dramatic. In long-term studies of bilateral pallidal stimulation described above, hardware failures were the most commonly reported adverse events, including unilateral or bilateral lead fracture. These appear to be more frequent in patients with dystonia than in other movement disorders.

**SUMMARY AND CONCLUSIONS**

Deep brain stimulation produces marked and long-lasting improvement in motor function and disability in patients with hyperkinetic disorders. In patients with essential tremor, stimulation usually targets the VIM of the thalamus. Reduction in tremor is most closely related to stimulation frequency and voltage, whereas pulse width has little effect on treatment outcome. In patients with dystonia, stimulation typically targets the GPi or STN. Long-term prospective clinical trials demonstrated significant reductions in motor severity rating scale scores. Selecting patients for DBS requires careful consideration of a range of factors, including the specific clinical presentation, treatment history, and social support. Areas of current investigation include optimal stimulation programming, intraoperative mapping, and the long-term efficacy and safety of stimulation.

**REFERENCES**


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