Movement Disorders

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Movement disorders are conditions that produce either reduced or excessive movement. Neurologic disorders that result in a paucity or slowness of movement are termed *hypokinetic* disorders. The category of hypokinetic disorders is represented by Parkinson disease and other causes of parkinsonism. *Hyperkinetic* disorders are characterized by excessive, involuntary movements. Hyperkinetic disorders can usually be placed into one of five main categories of abnormal movement: dystonia, chorea, tremor, myoclonus, or tic.

Abnormal movements may be difficult to recognize or categorize because of their unusual appearance, complexity, subtlety, or variability. Movement disorder specialists tend to isolate or reduce abnormal movements to their unitary components, but often it is the pattern of the movement and its body part distribution that provides the important diagnostic clue. In addition, many diseases cause abnormal movements that can be fit into two or more categories or abnormal movement phenomenology. Table 15–1 provides descriptions of the main categories of movement disorders.

There are many other types of abnormal movements that do not fit cleanly into a simple classification of phenomenology. *Athetosis*, meaning "no fixed posture," was first coined in reference to postanoxic birth injury to denote a quivering "fibrillary" movement of the limbs and digits. In modern usage, the term describes a slow, continuous, writhing movement that bears similarities to both chorea and dystonia. *Ballism* refers to large-amplitude random flinging movements of the limbs and represents a proximal form of chorea. Unilateral ballism is termed *hemiballism* and is most often caused by an infarct of the contralateral subthalamic nucleus. *Akathisia*, meaning "inability to sit," describes inner restlessness and intolerance of remaining still, together with repetitive fidgeting, squirming, and pacing movements.

Many, but not all, movement disorders result from disordered function of the basal ganglia, a group of interconnected subcortical nuclei. The basal ganglia comprise the substantia nigra, putamen, caudate, globus pallidus, and subthalamic nucleus, making up an extrapyramidal motor control system with extensive, reciprocal connections to the thalamus, cortex, brainstem, and cerebellum.

Many movement disorders are treated symptomatically, using agents that suppress or reduce unwanted movements, but in some cases therapies are available that address the underlying pathophysiology. In recent decades, treatment options including pharmacologic and surgical approaches have expanded, thanks to advances in basic sciences such as genetics and neurophysiology. In the sections that follow, the major movement disorder syndromes are described, with an emphasis on clinical diagnosis and treatment.

PARKINSONISM & PARKINSON DISEASE

ESSENTIALS OF DIAGNOSIS

- Tremor at rest
- Bradykinesia
- Rigidity
- Loss of postural reflexes
- Flexed posture
- Freezing

General Considerations

The term *parkinsonism* may be used when a patient exhibits one or more of the following findings: tremor at rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture, and freezing. Two of these findings, at least one of which must be tremor at rest or bradykinesia, are required to make a diagnosis of definite parkinsonism. Parkinson disease (PD) makes up 80% of cases of parkinsonism. PD has a prevalence of about 160 cases per 100,000 people and an incidence of

Table 15–1. General classification of abnormal movements.

	Category of Movement	Description and Associated Clinical Features	Differential Diagnosis
Hypokinetic	Parkinsonism	Akinesia/bradykinesia, Rigidity Tremor at rest Postural instability Gait freezing Flexion posture	Parkinson disease Diffuse Lewy body disease Atypical neurodegenerative Parkinson syndromes: Progressive supranuclear palsy (PSP), multiple systems atrophy (MSA), corticobasoganglionic degeneration (CBGD) Hydrocephalus Vascular parkinsonism Neuroleptic-induced parkinsonism Wilson disease
Hyperkinetic	Dystonia	Torsional movements that are partially sustained and produce twisting postures	Idiopathic or primary dystonia Dopa-responsive dystonia Anoxic-hypoxic injury Trauma Post-encephalitic dystonia Tardive dystonia
	Chorea	Random, quick, unsustained, purposeless movements that have an unpredictable, flowing pattern	Huntington disease Neuroacanthocytosis Post-infectious chorea Drug-induced chorea Vascular chorea Autoimmune chorea Chorea gravidarum
	Tic	Stereotyped, automatic purposeless movements and vocalizations	Tourette syndrome Cerebral palsy/developmental delay syndromes Autism Huntington disease
	Myoclonus	Sudden, shock-like movements	Physiologic myoclonus Essential myoclonus Metabolic encephalopathy Postanoxic myoclonus Progressive myoclonic epilepsy
	Tremor	Repetitive oscillation of a body part	Essential tremor Physiologic tremor Parkinson tremor Cerebellar tremor

about 20 cases per 100,000 people per year. Prevalence and incidence increase with age. Prevalence at age 70 is about 550 cases per 100,000 people, with an approximate incidence of 120 cases per 100,000 people per year. The mean age of symptom onset is 56 years in both sexes. However, the age range is wide, and young-onset PD (occurring in patients younger than 40 years) is not infrequent. PD is nearly twice as common in men as in similarly aged women. Family history of PD appears to be associated with an increased risk for development of PD, and mutations in identified PD genes account for 5–40% of cases depending on an individual's ancestry. Most of the remainder of cases are thought to be etiologically complex, resulting from gene–environment and gene–gene interactions.

Pathogenesis

The key motor symptoms of PD result from degeneration of dopamine [DA]-producing neurons within the pars compacta of the substantia nigra and norepinephrine [NE] cells of the locus coeruleus in the brainstem. However, PD is a complex clinical disorder that includes various nonmotor manifestations including impaired olfaction, autonomic dysfunction (eg, constipation, orthostatic hypotension), sleep disturbance (eg, rapid-eye movement [REM] behavior disorder), and alterations in mood and cognition. Underlying these clinical symptoms (many of which may precede overt motor signs) is pathology involving neurons outside the substantia nigra (eg, medullary and olfactory nuclei).

The pathologic hallmark of PD is the presence of eosinophilic cytoplasmic inclusions, termed *Lewy bodies,* within many of the surviving neurons. When symptoms become clinically evident, 60% of dopaminergic neurons in the substantia nigra already have been lost, and the basal ganglia (striatal) dopamine level has decreased by 80%. The precise cause of degeneration of dopaminergic cells within the substantia nigra is unknown in most individuals, but recent advances in molecular genetics have clarified genetic influences that contribute to the development of neuronal toxicity and parkinsonism in highly penetrant, autosomal dominant or autosomal recessive familial PD. Mutations in six genes (*SNCA, LRRK2, PRKN, DJ1, PINK1*, and *ATP13A2*) have conclusively been shown to cause familial parkinsonism. In addition, common variations in three genes (*MAPT, LRRK2*, and *SNCA*) and loss-of-function mutations in *GBA* have been well validated as susceptibility factors for PD. These genes encode proteins such as α-synuclein, parkin, and DJ-1, which are involved in folding, trafficking, and clearance of intracellular proteins and in maintaining mitochondrial function. Gene mutations result in mishandling of intracellular proteins, increased oxidative stress, free-radical formation, and energy depletion within the cell, causing oxidative damage and cell death. See Table 15–2 for a description of the gene mutations involved in PD. A currently influential hypothesis posits that PD results from the spread of α-synuclein from one neuron to another in a manner resembling the behavior of prions.

Prevention

In PD, preventive strategies have focused on neuroprotection of healthy dopamine-producing cells. However, no drug or dietary supplement has been shown with certainty to have neuroprotective or restorative benefits, despite well-controlled clinical trials of various agents including monoamine oxidase (MAO)-B inhibitors, coenzyme Q_{10}, and vitamin E.

Clinical Findings

A. Symptoms and Signs

The cardinal motor findings of PD include resting tremor, bradykinesia, rigidity, loss of postural reflexes, flexed posture, and freezing. Onset of symptoms is insidious and usually unilateral. Progression is usually slow.

1. Resting tremor and bradykinesia—These are the most characteristic motor features of PD. Tremor at rest with a frequency of four to six cycles per second is the presenting symptom in 70% of patients. Classically, resting tremor remains in one limb or asymmetrically in the ipsilateral arm and leg for months or years, but over time may generalize to all limbs. Although resting tremor usually involves distal limbs, it may also affect the muscles of the lips, tongue, jaw, and trunk. Occasionally the tremor is felt as an inner tremor before it can be seen. Typically, the tremor disappears with action of the involved limb and reemerges

Table 15–2. Parkinson disease genes.

Gene Mutation	Inheritance	Phenotype	Pathology
SNCA	AD	Early-onset rapidly progressive parkinsonism with dementia; overlap with DLBD and MSA	α-Synuclein Lewy bodies, frequent tau inclusions, neuronal loss in brainstem [LC and SNpc], and hippocampus
Parkin	AR	Early-onset parkinsonism, with slower course; sleep benefit, dystonia, hyperreflexia, levodopa-responsive, prone to dyskinesias	SNpc neuronal loss with absent Lewy bodies
PINK1	AR	Early-onset PD, with psychosis	Lewy body pathology, SNpc neuronal loss, sparing LC
DJ-1	AR	Early-onset parkinsonism, with tremor, falls, poor response to levodopa, dementia; rare	Sever SN and LC neuronal loss, prominent diffuse Lewy bodies, including cortex
LRRK2	AD	Late onset, tremulous PD Most prevalent monogenic cause of PD; most common mutation G2019S	Neuronal loss in LC and SNpc
GCH1		Childhood-onset dystonia-parkinsonism [dopa-responsive dystonia]	Absent Lewy bodies
GBA	AR	Typical levodopa-responsive PD, earlier onset, common cognitive impairment, prevalent among Ashkenazi Jews	LB pathology, cortical involvement

AD = autosomal dominant; AR = autosomal recessive; DLBD = dementia with Lewy bodies; GBA = glucocerebrosidase; LC = locus coeruleus; LRRK2 = leucine-rich repeat kinase 2; MSA = multiple system atrophy; PD = Parkinson disease; SNCA = α-synuclein; SNpc = substantia nigra, pars compacta.

with maintained posture. Stress, excitement, and walking can increase the tremor.

Bradykinesia manifests as a slowness in activities of daily living, production of movement, and reaction time and contributes to lack of automatic movement. Clinically, patients exhibit impaired fine motor movements, loss of facial expression, reduced arm swing when walking, and flexed (stooped) posture. Reduced amplitude of movement is most evident with repetitive movements such as finger or toe tapping. Hypomimia (decreased facial expression) results in decreased blink rate and loss of facial gestures. Other signs of bradykinesia include quiet voice (hypophonia), tachyphemia, sialorrhea, micrographia, and difficulty rising from a seated position.

2. Rigidity—Patients with PD have a sustained increased resistance to movement of a limb when that limb is passively extended, flexed, or rotated. Often cogwheeling can be appreciated, reflecting tremor superimposed upon rigidity. The rigidity may occur proximally at the neck, shoulders, or hips or distally at the elbows, wrists, knees, and ankles. Shoulder pain or stiffness is a frequent initial manifestation of PD and is often misdiagnosed as a rotator cuff injury, arthritis, or bursitis.

3. Loss of postural reflexes—A sign of advancing disease, loss of postural reflexes is evident as spontaneous retropulsion or inability to maintain balance when pulled from behind. Early in the course of the disease postural reflexes are preserved.

4. Freezing—This symptom, which refers to brief episodes of inability to initiate stepping, can be one of the most disabling symptoms of PD, and it may prove resistant to levodopa treatment. Also referred to as *motor blocks,* freezing typically occurs on initiation of walking, upon turning, or when walking through narrow passages, crossing streets, or approaching a destination or target, such as a chair. Patients experience inability to move their feet, as if glued to the ground, lasting seconds. Freezing that occurs early or predominantly in the course of disease should raise suspicion of an alternative diagnosis such as an atypical parkinsonian syndrome. *Festination* can occur during walking; patients take faster and faster steps and step size becomes smaller. Freezing, festination, and loss of postural reflexes are important causes of falling in patients with PD.

5. Nonmotor symptoms—Nonmotor symptoms occur frequently in patients with PD and some (eg, depression, anxiety, impaired olfaction, constipation, akathisia, REM behavior disorder) may precede overt motor signs by years. Cognitive changes are common and include slowed cognitive functioning (bradyphrenia); prolonged time to verbalize thoughts may be prominent. Dementia eventually occurs in 20–40% of patients with PD (for further discussion, see Chapter 9). Behavioral symptoms include personality changes, depression, reduced attention span, and visuospatial impairment. Sensory symptoms include pain, burning, and tingling. Autonomic disturbances include constipation, impotence, low blood pressure, and inadequate bladder emptying. Nonmotor symptoms can cause significant impairment and should be sought and treated as necessary.

B. Laboratory Tests and Imaging Studies

To date, there is no blood or cerebrospinal fluid (CSF) test that can diagnose PD. Similarly, there is no biological marker that can diagnose presymptomatic PD. Certain neuroimaging studies can be useful in confirming a diagnosis of PD. Routine magnetic resonance imaging (MRI) is typically normal in patients with PD. Single-photon emission computed tomography (SPECT) using ^{123}I-ioflupane permits visualization of the density of dopamine transporters in the basal ganglia; it is approved by the US Food and Drug Administration (FDA) for differentiating PD, in which dopamine transporter density is reduced, from essential tremor (see below), in which it is normal. However, this modality cannot distinguish PD from atypical parkinsonian syndromes (see below). Another imaging modality which can be of use is positron emission tomography (PET) imaging of the brain using ^{18}F-fluorodopa, which shows significant decreases in fluorodopa uptake in the basal ganglia of patients with PD. In general, a diagnosis of PD can be made clinically without neuroimaging studies.

Differential Diagnosis

The diagnosis of PD is based on history, clinical examination, and the absence of incompatible clinical, laboratory, or radiologic abnormalities. No single feature absolutely confirms or excludes the diagnosis of PD. Initial response to levodopa, which is often dramatic, is expected in PD, but is not specific as it can also occur early in the course of atypical parkinsonian syndromes.

Specific features that suggest the presence of an *atypical parkinsonian syndrome* rather than PD include symmetric onset of symptoms; absence of tremor; early gait abnormalities, including early falls and prominent freezing; early postural instability; dementia that precedes motor symptoms or occurs within the first year; corticospinal signs; cerebellar signs; abnormal eye movements other than restricted upward gaze; and symptomatic orthostatic hypotension.

Other major causes of parkinsonism are listed in Table 15–3. Drugs that block dopamine receptors (typical and atypical neuroleptics, certain antiemetics) or deplete striatal dopamine (reserpine, tetrabenazine) cause *drug-induced parkinsonism*; after the causative drug is stopped the symptoms usually improve slowly and resolve in most but not all cases. Anticholinergic drugs can improve parkinsonism caused by antidopaminergic drugs.

Table 15–3. Major parkinsonian syndromes.

Primary Idiopathic Parkinsonism
Parkinson disease (sporadic and familial)
Secondary Parkinsonism
Drug-induced (dopamine antagonists and depletors)
Hydrocephalus (normal-pressure hydrocephalus)
Trauma
Tumor
Vascular (multi-infarct state)
Metabolic (hypoparathyroidism)
Toxin (mercury, manganese, carbon monoxide, cyanide, MPTP)
Infectious (postencephalitic)
Hypoxia
Atypical Parkinsonian Syndromes
Progressive supranuclear palsy
Corticobasal degeneration
Multiple system atrophy:
• Shy-Drager syndrome
• Striatal nigral degeneration
• Olivopontocerebellar atrophy
Dementias
Diffuse Lewy body disease
Alzheimer disease
Inherited Degenerative Diseases
Wilson disease
Huntington disease
Neuroacanthocytosis
Hallervorden-Spatz disease

MPTP = methylphenyltetrahydropyridine.

Normal-pressure hydrocephalus causes a parkinsonian gait disorder notable for short, shuffling, or magnetic steps and loss of postural reflexes. These symptoms are accompanied by dementia and urinary incontinence that develop over time. Imaging of the brain reveals grossly enlarged ventricles. Diagnosis is confirmed by removal of CSF that results in significant improvement of gait; cognitive dysfunction and urinary incontinence are less likely to respond.

Lower-body parkinsonism may also be caused by vascular disease. *Vascular parkinsonism*, a slowly progressive gait disorder with freezing and loss of postural reflexes, results from multiple lacunar infarcts that are easily seen on MRI. Response to levodopa is not significant, and tremor is rare.

Parkinsonism also occurs in diffuse Lewy body disease, Alzheimer disease, Huntington disease, and Wilson disease. Early, mild PD is commonly misdiagnosed as essential tremor. Depression not only frequently complicates PD, but when severe can mimic parkinsonism.

Treatment

A. Pharmacotherapy

PD is a progressive neurodegenerative disease. No medication has been proven definitively to stop, slow, reverse, or prevent the progression of disease, although several have been evaluated in clinical trials with largely disappointing results. Therefore, current therapeutic strategies rely upon medications that improve symptoms, with the goal of allowing the patient to continue functioning independently for as long as possible. Treatment must be individualized to the patient's symptoms and stage of disease. Deciding which drugs to use and when to use them remains one of the greatest challenges of treating PD patients. Physicians typically adjust medications and dosages over the course of a patient's disease as new symptoms develop and adverse effects of drugs or loss of efficacy supervene.

Because striatal (basal ganglia) dopamine deficiency causes the main motor symptoms of PD, replacement of dopamine with dopaminergic agents is the major pharmacologic strategy. Nondopaminergic agents such as anticholinergics, antiglutaminergics, and muscle relaxants are also used to treat motor symptoms (Table 15–4).

1. Levodopa—Levodopa is the most potent agent for the symptomatic treatment of PD. In early, mild PD, it effectively ameliorates the cardinal motor symptoms, leading to the notion that clinical response to levodopa is diagnostic. However, adverse effects, including the development of dyskinesias (involuntary movements) and motor fluctuations, can limit its usefulness. After 5 years of levodopa therapy, more than 50% of patients develop fluctuations, including wearing off and sudden offs, and dyskinesia; these complications of treatment are thought to represent both pre- and postsynaptic changes related to disease progression in the setting of levodopa exposure. Theoretical concerns that levodopa itself may be neurotoxic (eg, through free radical

Table 15–4. Medications used in the treatment of parkinson disease.

Class	Group	Drug
Dopaminergic agent	Dopamine precursor	Levodopa (with carbidopa)
	Dopamine agonist	Bromocriptine, pramipexole, ropinirole, amantadine, apomorphine
	COMT inhibitor	Entacapone, tolcapone
	MAO-B inhibitor	Selegiline, rasagiline
Nondopaminergic agent	Anticholinergic	Trihexyphenidyl, diphenhydramine, amitriptyline
	Antiglutaminergic	Amantadin
	GABAergic drug	Lorazepam or clonazepam
Atypical neuroleptic	Serotonin and dopamine antagonist	Quetiapine

COMT = catecholamine O-methyl transferase; GABA = γ-aminobutyric acid; MAO = monoamine oxidase.

formation) have been debunked. Although levodopa has been prescribed for more than 30 years, its long-term effect on disease progression remains unknown.

There remains a lack of consensus about when treatment with levodopa should be initiated in patients with mild-to-moderate parkinsonism. Because of the probability of developing motor complications within the first 5 years of starting levodopa, many neurologists do not use levodopa as a first-line agent and prescribe less potent agents such as MAO-B inhibitors, amantadine, and dopamine agonists, often as monotherapy, in the mild stages of disease. Indications for starting levodopa include disabling symptoms and signs such as postural instability and falling. Moderately severe PD (ie, patients with bilateral motor symptoms and some postural instability but who remain physically independent) and a decline in the ability to carry out activities of daily living may also be indications for starting levodopa therapy. If patients are unable to tolerate dopamine agonists or do not obtain significant symptomatic benefit from a dopamine agonist in combination with nondopaminergic agents, initiation of levodopa therapy should be considered. Many patients older than 70 years of age and those with cognitive decline often do not tolerate dopamine agonists or nondopaminergic agents, and early use of levodopa should be considered for these patients as well. Other neurologists routinely use levodopa as first-line therapy even in early PD, citing studies that show superior benefit on motor symptoms and lower rates of discontinuation due to adverse effects compared with levodopa-sparing strategies.

Levodopa is converted to dopamine in the brain by amino acid decarboxylase. Pharmaceutical levodopa is combined with a peripheral dopamine decarboxylase inhibitor such as carbidopa, which inhibits the peripheral conversion of levodopa to dopamine and permits a greater amount of levodopa to cross the blood–brain barrier. As a result, the amount of levodopa that reaches the brain is greater, and peripheral dopamine-induced side effects such as anorexia, nausea, and vomiting.

Carbidopa-levodopa is available in standard preparations that contain a fixed ratio of each drug, 10 mg carbidopa to 100 mg levodopa (10/100), 25 mg carbidopa to 100 mg levodopa (25/100), and 25 mg carbidopa to 250 mg levodopa (25/250). A controlled-release formulation is available in ratios of 25 mg carbidopa to 100 mg levodopa (25/100) or 50 mg carbidopa to 200 mg levodopa (50/200). Treatment is usually started by gradually increasing the dosage until one tablet of carbidopa-levodopa 25/100 is taken three times a day, preferably in the morning, early afternoon, and early evening for maximum benefit. Taking the medication with meals helps prevent gastrointestinal upset, although protein intake may compete with levodopa transport in the duodenum. The dosage can be gradually titrated to symptomatic benefit. Long-acting controlled-release preparations of carbidopa-levodopa (Sinemet CR) provide a slower onset of effect, less bioavailability, and longer duration of effect than regular carbidopa-levodopa. Despite the theory that controlled-release levodopa formulations should provide a more constant level of bioavailable dopamine to the basal ganglia, thus reducing the frequency of motor complications, studies have failed to show that initial therapy with controlled-release formulations of levodopa decreased the development of motor fluctuations. Supplemental carbidopa can be prescribed as Lodosyn. In 2015, the FDA approved an enteral suspension of carbidopa/levodopa (Duopa) that is continuously infused into the jejunum and can be useful in patients experiencing motor fluctuations because it provides a continuous steady-state infusion of carbidopa-levodopa. However, the technology is subject to complications such as infection related to the catheter, tubing, and hardware.

Adverse effects of levodopa therapy include anorexia, nausea, vomiting, confusion, drowsiness, hypersomnolence, vivid dreams, nightmares, hallucination, postural hypotension, and cardiac arrhythmias. The development of central nervous system (CNS) adverse effects such as hallucinations is often dose-related and may require reduction in the dose of levodopa at the expense of worsening parkinsonian symptoms.

2. Dopamine agonists—After levodopa, the dopamine agonists are the most powerful antiparkinson medications. Dopamine agonists are synthetic compounds that stimulate striatal dopamine receptors. Although initially used as add-on therapy in patients receiving levodopa, the agonists are also commonly used first-line as monotherapy in patients with mild PD. Many neurologists do not prescribe dopamine agonists for patients older than 70 years of age because these patients are more likely to develop confusion, sleepiness, and psychosis from these medications. Because levodopa gives the greatest symptomatic benefit for the lowest risk of adverse effects compared with other agents, levodopa is often used as initial therapy in patients older than 70, especially those with preexisting cognitive decline. However, in patients with PD who are older than 70 but otherwise mentally and physically younger than this age, therapy with a dopamine agonist should be considered.

Studies of dopamine agonists as primary monotherapy in early PD show that drug-induced dyskinesias and motor fluctuations occur infrequently in these patients compared with those receiving levodopa monotherapy. However, monotherapy with a dopamine agonist is rarely sufficient for adequate symptomatic treatment after 3 years. Initial treatment of mild PD with dopamine agonists may give satisfactory reduction of PD symptoms while allowing for a delay in the initiation of levodopa therapy. Starting with a dopamine agonist also allows for a reduced dosages of levodopa used in combination with dopamine agonists when monotherapy with an agonist is no longer sufficient for symptomatic control. These benefits need to be weighed against its relative lesser potency and greater risk of certain side effects compared with levodopa.

Dopamine agonists include the oral agents pramipexole (Mirapex) and ropinirole (Requip), both of which are available in immediate-release and extended-release formulations, and the transdermal patch rotigotine (Neupro). They have been noted to cause sleep attacks (including when driving) and impulse control disorders such as gambling and shopping; other side effects include nausea, vomiting, sleepiness, peripheral edema, orthostatic hypotension, and psychotoxicity, including illusions, hallucinations, and mania. These symptoms stop when the drug is decreased or gradually stopped.

All dopamine agonists should be started at very low doses and increased gradually to reduce the risk of adverse affects. Drug selection is often made based on ease of titration and clinician experience. Patients respond individually to these medications, and if adverse effects develop from one agonist, another can be tried. If a sufficient therapeutic response is not attained with agonist monotherapy, other agents such as amantadine, trihexyphenidyl, or an MAO-B inhibitor can be added. If none of these medications is tolerated or efficacious, treatment with levodopa may be required.

Apomorphine is a nonergot dopamine agonist that is available for subcutaneous injection to rapidly treat sudden, severe, disabling off periods. Dosing must be titrated slowly and under the supervision of a physician. Side effects include severe nausea, profound hypotension, dyskinesias, and hallucinations. Because severe nausea and vomiting occur at recommended doses of apomorphine, an antiemetic such as trimethobenzamide must be used in conjunction with this medication.

3. Other dopaminergic agents

A. Selegiline, rasagiline, safinamide—These drugs are selective MAO-B inhibitors that increase dopamine by impairing its metabolism via MAO-B. This mechanism of action gives these agents their mild symptomatic effect. There are some data suggesting possible neuroprotective effects for selegiline and rasagiline, but these apparent effects are questionable because of methodologic factors and, if present, are small in magnitude.

MAO-B inhibitors generally are well tolerated and can be used as initial therapy in patients with very mild symptoms or as add-on therapy. The dosing of selegiline (Eldepryl) is 5–10 mg every day. Dosing should not exceed 10 mg/day because of risks associated with MAO enzyme inhibitors and ingestion of foods containing tyramine. Dosing of rasagiline (Azilect) is 0.5–1 mg once a day. Safinamide (Xadago) is taken 50–100 mg daily.

Coadministration with serotonergic agents, including many antidepressants, may lead to serotonin syndrome. This adverse interaction appears to be very uncommon but can occur, especially when doses are high. Because depression is so common in PD, cautious use of antidepressants with vigilance for symptoms of serotonin syndrome is advised. Other contraindicated drugs include meperidine, tramadol, methadone, propoxyphene, dextromethorphan, and St. John's wort. One of the metabolites of selegiline is an amphetamine, which may result in improved alertness but may also cause insomnia. Other side effects include dyskinesias, tremor, confusion, and psychosis.

B. Amantadine—This drug exerts its anti-PD effects through its mild dopaminergic (augmenting release and possibly inhibiting reuptake), anticholinergic, and antiglutaminergic properties. Amantadine (Symmetrel) is effective in both mild and advanced PD. In mild PD, amantadine can reduce symptoms of PD, especially tremor. In advanced PD, amantadine is a useful adjunct to therapy with levodopa and dopamine agonists. It is also effective in decreasing levodopa-induced dyskinesias. Side effects include peripheral edema, confusion, livedo reticularis, rash, and visual hallucinations. The usual dosage is 100 mg twice a day; doses up to 400 mg/day can be used. A long-acting form of amantadine (Gocovri) was recently approved for treatment of dyskinesia.

C. Entacapone—This drug is used in conjunction with levodopa to extend "on" time (duration of action of each dose of levodopa) by inhibiting the enzymatic conversion of levodopa to its metabolite. This results in increased synaptic levels of dopamine. Side effects include diarrhea, dyskinesia, and orange discoloration of urine. Entacapone (Comtan) comes in a 200-mg tablet and is taken simultaneously with levodopa. A formulation that contains 200 mg entacapone and various dosages of levodopa (50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg) with a proportionate amount of carbidopa in one tablet is available as Stalevo.

D. Tolcapone—Tolcapone has the same mechanism of action and therapeutic effect as entacapone; however, tolcapone can cause fulminant hepatitis resulting in death, and explosive diarrhea. Although hepatitis is a rare adverse effect, patients require baseline and biweekly liver transaminase profiles to monitor hepatic function. Tolcapone should not be used except when fluctuations are disabling and other drugs fail.

4. Nondopaminergic agents—Anticholinergic drugs such as trihexyphenidyl (Artane) and benztropine (Cogentin) are mild anti-PD drugs used primarily as monotherapy or in conjunction with dopaminergic medications in tremor-predominant PD. Bradykinesia and rigidity may also be minimally improved with anticholinergic therapy. Peripheral and central side effects can be prominent, including confusion, forgetfulness, blurred vision, constipation, dry mouth, urinary retention, hallucinations, and psychosis. Such side effects are especially problematic in older patients, and therefore anticholinergic drugs are generally avoided in this population. In such patients who might benefit from adjunctive therapy with an anticholinergic, a weaker anticholinergic such as diphenhydramine or amitriptyline can be used instead of trihexyphenidyl.

Benzodiazepines, such as lorazepam, with moderately long half-lives, used in small doses (0.5–1 mg twice a day), can be useful in treatment of anxiety that can result from and further complicate significant motor fluctuations.

Hallucinations are a common side effect of dopaminergic therapy and more prevalent with dopamine agonists than with levodopa. The safest approach for patients experiencing hallucinations and psychosis is to lower the dose of dopaminergic therapy, but motor symptoms may not permit a reduction in dose, in which case antipsychotic medications that do not block dopamine receptors can be tried. The most commonly used agent for treatment of mild to moderate hallucinations is quetiapine (Seroquel). Low-dose quetiapine (12.5–25 mg at bedtime) may also be used to treat insomnia, which often occurs in patients with PD. Pimavanserin (Nuplazid) is approved for treatment of psychosis in PD. If these are not tolerated or are ineffective, clozapine (Clozaril) is usually effective. However, the risk of bone marrow suppression makes clozapine a difficult medicine to use.

B. Surgery

Neurosurgery for the symptoms and signs of PD has proven effective and long-lasting. The application of stereotactic lesion and stimulation techniques to PD, essential tremor, and dystonia began serendipitously in 1952 with the inadvertent ligation of the anterior choroidal artery, which supplies the medial lentiform nucleus and globus pallidus, resulted in the abolition of tremor in a patient with PD. In the decades following, and before the advent of levodopa, neurosurgical lesioning procedures targeting the globus pallidus, thalamic nuclei, and other parts of the basal ganglia were used to improve the symptoms of PD.

The development of **deep brain stimulation** (DBS) in the late 1990s revolutionized the field of functional neurosurgery and the treatment of advanced PD. Electrodes implanted into the subthalamic nucleus or the globus pallidus were found to provide relief of tremor, rigidity, bradykinesia, Parkinson-associated dystonia, and levodopa-induced dyskinesias. DBS proved especially advantageous to the patient experiencing "wearing off" motor fluctuations and dopaminergic dyskinesias, two complications of chronic medication treatment that cannot be readily helped using medication adjustment alone.

Surgical candidates are patients with idiopathic PD who are not demented or actively depressed and who respond, however briefly, to individual doses of levodopa; such a response is necessary in order to determine that a patient does not have an atypical parkinsonian syndrome, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or post-traumatic or vascular parkinsonism. See Table 15–5 for a description of candidates for DBS. When successful, DBS results in reductions in "off" time of motor fluctuations and in dyskinesias. (For a list of symptoms of PD that respond to DBS, see Table 15–6.)

Table 15–5. Candidates for deep brain stimulation.

Ideal Candidate	Poor Candidate
Typical Parkinson disease	Atypical parkinsonism: PSP, MSA, vascular parkinsonism
Excellent response to individual doses of levodopa, even if short-lived	Poor or absent response to levodopa, even in high dose
Dopaminergic dyskinesias, "wearing off" motor fluctuations, or medication-refractory tremor	Postural instability, gait freezing
Normal cognition	Dementia, apathy, or severe depression
Good general health	Severe medical problems
Excellent support network	Poor or absent support network

MSA = multiple system atrophy; PSP = progressive supranuclear palsy.

DBS can also suppress a medication-refractory tremor in PD. Medication dosages can often be lowered postsurgically, reducing dopamine-induced dyskinesias or other side effects. With DBS, as opposed to stereotactic lesioning, stimulators are usually implanted bilaterally with the benefit of bilateral symptomatic improvement. DBS is reversible; pulse generators may be turned off or electrodes can be surgically removed without causing damage to brain tissue. Recent data have shown that DBS is better than best medical therapy in patients with moderately advanced symptoms, and there is a tendency in the literature and clinical practice to perform DBS surgery earlier in the course of the illness, before the onset of gait imbalance, freezing, or dementia. Proper patient selection by a neurologist with PD and DBS expertise is critical. Realistic expectations of the benefits of this surgical procedure are crucial for patients and families. Surgery is not curative and does not alter the progression of disease.

In recent years, the DBS field has advanced through refinements in battery technology and lead capability.

Table 15–6. Parkinson disease symptoms that respond to deep brain stimulation (DBS).

Symptoms That Respond to DBS	Symptoms That Do Not Respond to DBS
Tremor	Gait freezing
Rigidity	Postural instability, frequent falls
Bradykinesia	Postural deformity, camptocormia
Dystonia and dyskinesias	Hypophonia, tachyphemia
	Dementia, apathy

Further, a resurgence in stereotactic lesioning, using focused ultrasound and gamma knife radiosurgery, has occurred. Both techniques can accurately target the ventral intermediate (VIM) thalamus and ablate a disabling tremor, avoiding the placement of brain electrode, and attendant hardware, but these lesioning procedures can only be performed unilaterally and an off-target lesion will result in permanent injury.

Prognosis

PD is a neurodegenerative disorder that worsens slowly over years. The natural history of PD is influenced by the age at onset of disease, lifestyle, and medical therapy. Although there is no conclusive evidence that medical therapies slow the progression of disease, morbidity and mortality rates from PD have decreased with the use of levodopa. In addition to prolonging survival time, functional capacity and quality of life are significantly improved by thoughtful treatment with available medications.

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ATYPICAL PARKINSONIAN SYNDROMES

The atypical parkinsonian syndromes include progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy (Table 15–7). Early in their disease course, many patients are initially misdiagnosed with idiopathic Parkinson disease (PD). A lack of response to levodopa, early falls, early freezing (motor blocks), presence of cortical or corticospinal abnormalities on examination, and involvement of cranial nerve function distinguish these syndromes from PD. Notably, these syndromes progress rapidly and are difficult to treat.

PROGRESSIVE SUPRANUCLEAR PALSY

ESSENTIALS OF DIAGNOSIS

- Progressive parkinsonism
- Vertical supranuclear ocular palsy or slow vertical saccades
- Early onset of falling
- Axial rigidity

General Considerations

PSP is categorized as an atypical parkinsonian syndrome or Parkinson-plus syndrome. The prevalence of PSP is estimated at 1.39 cases per 100,000 people. Similar to PD, PSP occurs more frequently in men. The mean age of onset is 65 years.

Pathogenesis

The pathologic findings in PSP are distinctive for marked neuronal degeneration and neurofibrillary tangles and tau-positive astrocytes in basal ganglia and brainstem structures. The neurofibrillary tangles found in PSP, which contain the microtubule-associated protein tau, differ from those seen in Alzheimer disease and other neurodegenerative disorders.

Table 15–7. Atypical parkinsonian syndromes.

Syndrome	Parkinsonism Plus . . .	Neuroimaging Findings	
		PET	*MRI*
Progressive supranuclear palsy (PSP)	Impaired downgaze, neck and axial rigidity, early loss of postural reflexes	Hypometabolic basal ganglia and frontal cortex	Midbrain atrophy
Corticobasal degeneration (CBD)	Severe unilateral rigidity, alien limb phenomena, unilateral apraxia, unilateral cortical myoclonus, early dementia	Asymmetric cortical hypometabolism	Asymmetric parietal lobe atrophy
Multiple system atrophy (MSA) • Striatonigral degeneration • Shy-Drager syndrome • Olivopontocerebellar atrophy	Laryngeal stridor, increased deep tendon reflexes, dysarthria, absence of tremor Early, symptomatic orthostatic hypotension; urinary or fecal incontinence Cerebellar dysmetria and dysarthria	Hypometabolic basal ganglia and frontal lobes (seen in all MSA syndromes)	Brainstem atrophy (in all MSA syndromes)

MRI = magnetic resonance imaging; PET = positron emission tomography.

Loss of striatal (basal ganglia) neurons and their postsynaptic dopamine receptors explains the poor symptomatic response to levodopa and dopamine agonists.

Clinical Findings

A. Symptoms and Signs

The history is notable for early onset of falls, freezing, and parkinsonism. Common examination findings early in the course of disease include prominent axial rigidity, dystonic retrocollis, and facial dystonia, giving patients an angry or surprised look. Typical eye findings include supranuclear ocular palsy, causing impairment of vertical gaze (more commonly downgaze), and ocular square-wave jerks (small horizontal saccades alternately to the left and right). Patients may be unable to look downward voluntarily, yet reflex ocular movements remain normal. Speech may be nasal, dysarthric, and slow; phonation is dystonic, giving a raspy growl. Gait is wide-based, and postural reflexes are absent. As the disease progresses, dysarthria, dysphagia, and cognitive impairment occur. Cognitive impairment is notable for bradyphrenia, impaired verbal fluency, difficulty with sequential tasks, impulsivity, poor judgment, and unawareness of falling risk. Emotional lability, with inappropriate weeping or laughing, may occur. In some patients with facial dystonia, disabling blepharospasm may occur. Rest tremor is distinctly uncommon, and there is no effective response to levodopa.

B. Imaging Studies

CT or MRI scans of patients with PSP may show brainstem atrophy, particularly in the midbrain (giving rise to the "hummingbird sign"), and generalized cerebral atrophy. PET scanning with ^{18}F-deoxyglucose shows hypometabolism in the frontal cortex, and brainstem.

Differential Diagnosis

The major alternative diagnoses include PD, corticobasal degeneration, multisystem atrophy, vascular parkinsonism, and diffuse Lewy body disease.

Treatment

There is no specific treatment for PSP, and symptomatic improvement is difficult to obtain. Levodopa and other anti-PD medications should be tried but are rarely very effective. A combination of dextromethorphan/quinidine (Nuedexta) may help pseudobulbar affect (involuntary emotional expression disorder), and zolpidem (Ambien) has been reported to be beneficial for eye movements and motor function in PSP patients. Dystonia can be improved with botulinum toxin injections to affected muscles. Patients may opt for enteric feeding if dysphagia becomes severe.

Prognosis

Symptoms are steadily progressive, and death, often due to aspiration, usually occurs 5–10 years after onset of disease.

CORTICOBASAL DEGENERATION

ESSENTIALS OF DIAGNOSIS

- Parkinsonism
- Unilateral arm rigidity and dystonia
- Cortical sensory deficits

Clinical Findings

A. Symptoms and Signs

Patients with corticobasal degeneration often describe unilateral hand clumsiness with corresponding limb rigidity and bradykinesia. The onset is usually insidious, involving asymmetric parkinsonism, focal rigidity, and dystonia involving one arm, and cortical sensory deficits. Cortical sensory loss, apraxia, myoclonus, and alien limb phenomena (insuppressible, involuntary movements) occur in the affected limb. Patients may have coarse rest and action tremor. Speech becomes notably slurred and labored, causing disturbances in communication and language. Early features include falling and loss of postural reflexes. Other findings include hyperreflexia and the Babinski sign. Later in the course of the disease, both sides of the body are involved, disturbances of ocular motility occur, and dementia often develops.

B. Imaging Studies

CT and MRI scans may show asymmetric parietal lobe atrophy corresponding to the more affected side of the brain. Asymmetric frontoparietal atrophy helps to differentiate corticobasal degeneration from PSP. PET scans show reduced ^{18}F-fluorodopa uptake in the basal ganglia and asymmetric cortical hypometabolism.

Differential Diagnosis

The main alternative diagnoses are PD and PSP. Frontotemporal dementia, PSP, and sometimes Alzheimer disease can produce features resembling corticobasal degeneration, in which case the term *corticobasal syndrome* is applied.

Treatment & Prognosis

No effective treatment exists. Levodopa and other dopaminergic drugs are rarely effective. Clonazepam may improve myoclonus. Dystonia and rigidity may improve with botulinum toxin injections. Corticobasal degeneration progresses

more rapidly than PD, and mean survival is about 6 years after onset of symptoms.

MULTIPLE SYSTEM ATROPHY

ESSENTIALS OF DIAGNOSIS

- Parkinsonism
- Symptomatic orthostatic hypotension
- Cerebellar ataxia
- Poor therapeutic response to levodopa

General Considerations

MSA encompasses distinct subtypes that have overlapping clinical and prognostic features. These include the parkinsonian subtype (MSA-P, formerly striatonigral degeneration), the autonomic subtype (MSA-A, formerly Shy-Drager syndrome), and the cerebellar subtype (MSA-C, formerly olivopontocerebellar atrophy). Ten percent of patients with parkinsonian signs have MSA. In 100 patients with probable MSA (14 confirmed at autopsy), the median age of onset was 53 years, with a range of 33–76 years; 67 patients were men, and 33 were women.

Clinical Findings

A. Symptoms and Signs

Patients with MSA present with parkinsonism and additional characteristic clinical features. **MSA-P** is characterized by parkinsonism without tremor. Other features include dysarthria, dysphagia, laryngeal stridor, increased deep tendon reflexes, anterocollis, and early postural instability. Striatal neurons containing dopamine receptors are lost, resulting in a characteristically poor response to levodopa.

MSA-A is characterized by parkinsonism and symptomatic, autonomic dysfunction. Orthostatic hypotension may be severe, disabling, and difficult to treat. Other autonomic symptoms such as bladder and bowel dysfunction and impotence also occur. Brainstem, basal ganglia, preganglionic sympathetic neuronal, and cerebellar degeneration occurs in MSA. Occasionally, the basal ganglia are spared, accounting for unpredictable levodopa responsiveness.

MSA-C is characterized by parkinsonism and cerebellar symptoms. Degeneration of the pons, cerebellum, basal ganglia, and substantia nigra is present. If the basal ganglia are not severely degenerated, parkinsonism responds to levodopa therapy.

B. Imaging Studies

In MSA, T2-weighted MRI scans may show decreased signal intensity in the putamen as well as slit-hyperintensity in the lateral margin of the putamen. The "hot cross bun sign," cross-shaped hyperintensity in the pons on T2 axial views, may be present in MSA-C, representing degeneration of pontocerebellar tracts. PET scan shows hypometabolism in the striatum and cerebellum.

Treatment

Treatment is based on the approach used in PD. Dopaminergic medications should be tried for symptomatic relief. A trial of levodopa (up to 2 g/day, as tolerated, with carbidopa) should be given to assess for levodopa responsiveness. Although patients with MSA may initially respond to levodopa because of preserved basal ganglia function, symptomatic benefits are rarely sustained, and moderate or high doses of levodopa may exacerbate preexisting orthostatic hypotension. In patients with MSA-A, several methods are used to treat symptomatic orthostatic hypotension. Initially, increasing salt intake and wearing support hose may be beneficial. Drugs such as midodrine (ProAmatine), fludrocortisone (Florinef), or droxidopa (Northera) may eventually be required if hypotension becomes disabling. Cerebellar symptoms in MCA-C may respond to amantadine 100 mg, up to four times a day. Physical therapy with emphasis on balance, gait, and range of motion is critical for optimizing mobility. The symptoms of MSA respond poorly to deep brain stimulation.

Prognosis

MSA (all three syndromes) progresses rapidly compared with PD, and patients with prominent autonomic dysfunction have a worse prognosis. Many patients are wheelchair-bound or markedly disabled within 5 years of diagnosis. Mean survival rate in MSA is about 8–9 years after onset of symptoms.

ESSENTIAL TREMOR

ESSENTIALS OF DIAGNOSIS

- Action tremor of arms, head, and voice
- Family history of tremor (often)
- Absence of parkinsonism
- Transient improvement of tremor with alcohol ingestion

General Considerations

Essential tremor (ET) is a chronic, progressive neurologic condition characterized by action tremors that affect the hands as well as the legs, neck, and voice. The former descriptor *benign essential tremor* is not appropriate, because

the symptoms advance over time, sometimes to the point of disability. ET is more prevalent than PD or Alzheimer disease, affecting up to 10% in those older than 65 years of age. Onset is most common in persons in their early twenties or in later adulthood, but ET may occur at any age. Both sexes are equally affected. Most patients never seek medical attention, because the tremor remains mild. The etiology of ET is partly genetic. Many studies show that it is familial in 50–70% of patients, with autosomal dominant transmission. The pathobiology of ET implicates a disorder of cerebellar function.

Clinical Findings

A. Symptoms and Signs

ET is characterized by a 4–10-Hz symmetric action tremor of the arms. Action tremors includes postural tremors (maintaining a posture against gravity) and kinetic tremors (tremor that occurs with voluntary movement of the affected limb). Ninety percent of patients have arm and hand tremor, 30–50% have head tremor, 20% have voice tremor, and approximately 12% have leg tremor. ET is described as a monosymptomatic syndrome, yet up to 50% of patients have very subtle cerebellar signs, such as impaired tandem gait or mild ataxia. In more that 50% of patients, tremor can be transiently diminished by ingestion of alcohol. Common tasks affected by kinetic arm tremor include writing, drinking out of a full cup, and eating soup with a spoon.

Differential Diagnosis

ET is most frequently misdiagnosed as PD (Tables 15–8 and 15–9). Distinguishing features of ET include the absence of rest tremor; the symmetric onset of action tremor; and lack of parkinsonian features such as bradykinesia, rigidity, or loss of postural reflexes. In patients with ET, handwriting is large and tremulous rather than the tremulous micrographia seen in those with parkinsonism. A proximal tremor that reappears with the arms held in wing position is probably a reemergent PD tremor. ET patients have a fourfold increased risk of PD, resulting in the tremor-predominant condition essential tremor–Parkinson disease, or ET-PD.

It can be often difficult to distinguish between mild ET and enhanced physiologic tremor [EPT]; ET is chronic and EPT is episodic, often situational, and provoked by a stressor. Patients with head tremors may have dystonia, especially if the head tremor is isolated, and the tremor exhibits dystonic features: directionality, a null point or the stabilizing sensory trick ("geste antagoniste.") Cerebellar (intention) tremor can be differentiated from ET by the presence of cerebellar signs such as dysmetria and dysdiadochokinesis as well as by marked exaggeration of the tremor as the hand approaches the target (ie, with intention).

The leading alternative diagnosis for ET is exaggerated physiologic tremor, an action tremor that resembles ET except that it is occurs under stressors (anxiety) with fatigue,

Table 15–8. Essential tremor versus parkinson disease: phenomenology.

Phenomenology	Essential Tremor	Parkinsonian Tremor
Rest tremor—arms	Rarely; implies coexisting PD	Yes
Rest tremor—legs	No	Yes
Kinetic tremor	Yes	Minimally
Postural tremor	Tes	Minimally
Intention tremor (dysmetria at target)	Yes	No
Head tremor	Yes	No
Face and lip tremor	No	Yes
Tongue tremor	No	Yes
Jaw tremor	When mouth open or moving	When jaw is at rest
Voice	Tremulous	Hypophonic, tachyphemic
Postural instability	No	Yes
Ataxia; abnormal tandem	Frequent	Rare

PD = Parkinson disease.

Table 15–9. Essential tremor versus parkinson disease: clinical.

Clinical Pathophysiology	Essential Tremor	Parkinsonian Tremor
Age of onset	Bimodal: teens, middle life	50 to 65 years
Progession	May plateau for decades, later progressive	Progressive
Symmetry	Onset in both hands, usually worse in nondominant hand	Unilateral onset, asymmetrical
Spiral drawing	Large, tremulous, concentric	Small eccentric
Alcohol response	Yes (50%)	No
Family history	Yes (50%)	Less common
Medication	Propranolo, primidone, benzodiazepines, topiramate	Levodopa, anticholinergics, amantadine, dopamine agonists
Deep brain targets	Ventral intermediate thalamus, zona incerta	Subthalamic nucleus Globus pallidus interna

Table 15–10. Treatment of essential tremor.

Drug	Initial Adult Dose	Usual Effective Dose
Propranolol	20 mg/day	80–240 mg/day
Primidone	12.5–25 mg at bedtime	50–500 mg/day
Topiramate	12.5–25 mg/day	100–400 mg/day
Clonazepam	0.5 mg/day	2–4 mg/day
Gabapentin	100 mg	1200–1800 mg/day

or due to medication or stimulants. Tremorogenic agents include caffeine, methylphenidate, lithium, valproate, selective serotonin reuptake inhibitors, tricyclic antidepressants, β-adrenergic agonists, ephedrine, theophylline, corticosteroids, and tacrolimus. Hyperthyroidism can cause a symmetrical tremor that mimics ET. Action tremors occur in neuropathy causing weakness.

Treatment

Propranolol, a β-blocker, and primidone, an anticonvulsant, are the two first-line and most commonly used agents for treatment of ET (Table 15–10). Side effects may limit tolerability and necessitate switching to an alternate medication. Benzodiazepines (clonazepam, alprazolam) may be efficacious, perhaps by reducing the anxiety that exacerbates ET. The anticonvulsant gabapentin has been used as adjunct therapy in ET.

Chemodenervation using botulinum toxin improves limb tremor, head tremor, and voice tremor. Limitations of botulinum toxin therapy include excessive weakness at the site of injection and the short-lived nature of the response, necessitating reinjection every 3–6 months, depending upon the site.

For tremors that are disabling and refractory to medication, deep brain stimulation targeting the VIM thalamus or zona incerta or a stereotactic lesioning procedure may offer the only effective therapy. DBS has an advantage over a thalamotomy using focused ultrasound or gamma knife because lesioning procedures can only be performed unilaterally, and an off-target lesion may cause permanent grain injury. The lesioning procedures may be advantageous for patients who cannot undergo implantation of a brain electrode.

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DYSTONIA

ESSENTIALS OF DIAGNOSIS

- Sustained muscle contractions, often causing twisting movements or abnormal postures
- Varies in age of onset, anatomic distribution
- Can be primary, or can be a feature of an underlying neurologic disorder or exogenous insult
- When secondary, frequently accompanied by other abnormal movements or neurologic signs

General Considerations

Dystonia is a movement disorder characterized by relatively sustained and directional muscle contractions that produce abnormal postures or twisting and repetitive movements. The movements are usually longer in duration than those seen in other movement disorders (eg, chorea or myoclonus), involve the co-contraction of agonist and antagonist muscles, and tend to be repetitive or patterned, consistently involving the same muscle groups. A formal definition of dystonia, originally coined by Oppenheimer in 1991, can be paraphrased: Dystonia consists of sustained or intermittent muscular contractions that are patterned and torsional, resulting in abnormal twisting movements and postures. Unlike the quick, random movements of chorea, or the sudden shock-like movements of myoclonus, dystonia is patterned, directional, and sustained at the peak of contraction. In *action dystonia*, the dystonic movements are elicited only with voluntary movement. When dystonia is triggered only with particular actions, it is called *task-specific dystonia*; examples include writer's cramp and the embouchure dystonia of woodwind and brass musicians. Activation of dystonic movements by actions in remote parts of the body is called *overflow;* examples include leg dystonia while writing or axial dystonia with talking. Dystonia that is suppressed by voluntary activity is called *paradoxical dystonia*; for example, talking or chewing may suppress dystonia involving facial and oromandibular muscles (also known as *Meige syndrome*).

Factors that tend to exacerbate dystonia include fatigue and emotional stress, whereas the movements usually decrease with relaxation or sleep. Many patients discover a tactile or proprioceptive sensory trick (*geste antagoniste*) that minimizes the dystonia; for example, a patient with cervical dystonia may touch the chin. Severe dystonia is less likely to respond to these maneuvers, and joint contractures can occur when dystonia is long-standing.

The new classification of dystonia is the result of the discovery of several causative genes, which has reduced the previous categories "primary," "secondary," and "idiopathic" into a wide grouping of dystonia syndromes now known to result from defined genetic mutations and rooted in pathology. The new dystonia classification is anchored by two axes—axis I and axis II—as shown in Table 15–11. Axis I combines all of the prior clinical descriptors into a framework encompassing age of onset, body distribution, temporal pattern and associated clinical manifestations.

Dystonia is subclassified by anatomic distribution, by age of onset, and by etiology. In *focal dystonia*, the abnormal movements involve a single body region, whereas *segmental dystonia* affects two or more contiguous body parts. When *multifocal*, two or more noncontiguous body areas are involved. *Hemidystonia* affects one side of the body and is suggestive of a

Table 15–11. New dystonia classification.

Axis 1			Axis II	
Clinical features	Age of onset	Infancy (0–2 years) Childhood (3–12 years) Adolescence (13–20 years) Early adulthood (21–40 years) Late adulthood (>40 years)	Pathology	Evidence of degeneration (including iron or copper accumulation) Structural lesion (such as tumor, stroke, toxic exposure)
	Body distribution	Focal (single body region): Orbicularis oculi (blepharospasm) Larnynx (spasmodic dysphonia) Face (cranial) Neck (cervical dystonia) Arm/hand Foot Segmental: Face and neck Neck and arm Multifocal Generalized (usually involves trunk or both legs) Hemidystonia (usually caused by a focal basal ganglia lesion)	Inherited	Autosomal dominant Autosomal recessive X-linked Mitochondrial
	Temporal pattern	By disease course: Acute Chronic or persistent Static Progressive By variability: Paroxysmal Diurnal Task-specific	Acquired (due to a known specific cause)	Brain injury Infection Drug, Toxin Hypoxia Vascular Paraneoplastic Brain accumulation of iron (NBIA: PKAN due to mutation in PANK 1 or PANK 2 genes), neuroferritinopathy, aceruloplasminemia Wilson disease
	Associated features	Isolated (formerly "primary") except for tremor Combined (formerly "dystonia plus") Combined Associated with: • Other neurologic conditions • Other movement disorders • Other systemic manifestations	Idiopathic	Sporadic Familial (assumed genetic; mutation not yet detected)

secondary dystonia. *Generalized dystonia* involves the legs (or one leg and the trunk) plus at least one other area of the body.

Cervical dystonia is the most common of the focal dystonias. Various combinations of neck muscles may be involved to produce abnormal head positions, including horizontal turning (torticollis), tilting (laterocollis), flexion (anterocollis), or extension (retrocollis). Repetitive jerking of the head may resemble tremor, but can usually be distinguished by its directional preponderance. Approximately 75% of patients complain of neck pain. Less common than cervical dystonia are the focal dystonias that involve cranial muscles. *Blepharospasm* causes contraction of the orbicularis oculi; mild cases are characterized by increased blink rate with flurries of blinking, whereas more severely affected patients have visual impairment due to sustained forceful eye closure. *Spasmodic dysphonia* results from dystonia of the vocal cords; abnormal adduction, which causes a strained, strangled voice, is more common than abduction, in which the voice sounds whispering and breathy. In *oromandibular dystonia* there is abnormal activity in lower facial, tongue, jaw, and pharyngeal muscles that may interfere with speaking or swallowing. *Brachial dystonia* is a form of focal dystonia that may be primarily, or only, present with writing (*writer's cramp*); it is probably more common than is usually recognized. In about 15% of patients, there is spread from the dominant to the contralateral arm, at which point it is considered segmental bibrachial dystonia. Other segmental dystonias involve the cranial muscles (eg, *Meige syndrome*), sometimes in combination with neck muscles (*cranial-cervical dystonia*).

Age at onset is an important prognostic consideration, because patients with onset of dystonia in childhood or adolescence are likely to progress to generalized or multifocal dystonia, especially when the dystonia initially involves the leg.

Classification of a patient's dystonia by etiology is useful for prognosis, for guiding therapy, and for genetic counseling. In isolated dystonia, which may be familial or sporadic, no associated neurologic abnormalities (eg, dementia, ocular abnormalities, ataxia, spasticity, or paresis) are present. (An exception is tremor, which is common in patients with primary dystonia, especially cervical dystonia.) Isolated dystonia is distinguished from the *combined dystonias* (formerly "secondary" dystonia or "dystonia plus" or "symptomatic" dystonia) by the absence of signs other than dystonia as well as by the absence of an identified exogenous cause or brain degeneration. The combined dystonias include (1) the inherited *dystonia-plus* syndromes, which are similar to primary dystonia in that there is no evidence of brain degeneration, but signs other than dystonia are present (specifically myoclonus and parkinsonism); (2) inherited neurologic conditions associated with neuronal degeneration (eg, Huntington disease, Wilson disease, the spinocerebellar ataxias); (3) dystonia associated with PD and other parkinsonisms; and (4) dystonia due to environmental causes (eg, exposure to neuroleptics, stroke). Finally, dystonia may occur as a feature of other movement disorders, such as tic disorders and paroxysmal dyskinesias.

Most isolated (formerly "primary") dystonias are focal or segmental in distribution, with onset in adulthood. About 10% of patients with isolated dystonia have generalized dystonia, usually starting in childhood or adolescence (early-onset). DYT1, a major cause of early-onset dystonia, results from mutation of the gene *TOR1A* located on the long arm of chromosome 9 (9q34.1). *TOR1A* codes for torsinA, a heat-shock protein that binds ATP; in DYT1 dystonia, deletion of a GAG triplet from this gene results in loss of a glutamic acid residue from torsinA. This deletion is especially common in the Ashkenazi Jewish population, where its prevalence is 1 in 2000 persons. It is inherited in an autosomal dominant fashion, with reduced penetrance of 30%. DYT1 dystonia (formerly called *Oppenheim dystonia* or *dystonia musculorum deformans*) is now classified as early-onset, generalized, persistent, isolated, inherited and dominant disorder. It has a mean age at onset of 12.5 years and begins in a limb in 94% of cases. It tends to progress to generalized dystonia; as mentioned earlier, the probability of generalization is related to age and site of onset. A less common early-onset inherited primary dystonia is DYT6 dystonia due to heterozygous mutations in the gene *THAP1*. *THAP1* is a member of a family of cellular factors that share a conserved THAP (thanatos-associated protein) DNA binding domain. Dystonia due to *THAP1* often involves the arms and axial muscles but differs from DYT1 in that speech is also frequently affected due to oromandibular or laryngeal involvement. It may, however, mimic DYT1. Other loci for primary dystonia include DYT7 (late-onset autosomal dominant focal dystonia in a northwestern German family and DYT17 (early-onset autosomal recessive dystonia in a Lebanese sibship with segmental and generalized dystonia including dysphonia and dysarthria). The most common genetic dystonia syndromes are presented in Table 15–12.

The dystonia-plus syndromes include dopa-responsive dystonia, rapid-onset dystonia-parkinsonism, and myoclonus-dystonia. Perhaps the most important to recognize is *dopa-responsive dystonia* (DRD), or *Segawa disease*, as it is treated very effectively with levodopa. Typically, gait dysfunction (often appearing stiff-legged or spastic) begins in early or mid-childhood, and symptoms are worst late in the day and improve with sleep. Parkinsonism, including rigidity, bradykinesia, flexed posture, and loss of postural reflexes, may be prominent, making juvenile parkinsonism an important differential diagnosis. DRD has also been misdiagnosed as cerebral palsy. Girls are affected more often than boys. Onset in adulthood is uncommon, and may present as focal dystonia or parkinsonism. Most cases of DRD are caused by heterozygous mutations in the GTP-cyclohydrolase I (*GCH1*) gene located at 14q22.1 (DYT5); many different mutations have been identified, making genetic testing complex and expensive. The mutations impair the activity of GTP-cyclohydrolase I, which catalyzes the rate-limiting step in the synthesis of tetrahydrobiopterin, a necessary cofactor for tyrosine hydroxylase; tyrosine hydroxylase in

Table 15–12. Most common genetic dystonia syndromes.

Nomenclature	Inheritance	Locus	Gene Product	Phenotype
DYT1	AD	9q34.11	TOR1A, torsinA	Original "classic" Openheim phenotype, childhood-onset monosymptomatic disorder, usually begins in the limb, with generalization, prevalence in Ashkenazi Jews, 30% penetrance
DYT3	XR	Xq13.1	TAF1	"Lubag" X-linked dystonia-parkinsonism, Filipino
DYT4	AD	19.p13.3	TUBB4a, β-tubilin 4a	Generalized dystonia with spasmodic dysphonia
DTY5a	AD	14q22.2	GTP cyclohydrolase 1 [GCH-1]	Classic dopa-responsive dystonia (DRD; Segawa disease)
DYT5b	AR	11p15.5	Tyrosine hydroxylase [TH]	DRD, infantile parkinsonism
DYT6	AD	8p11.21	THAP1	Mixed dystonia (neck, limbs, generalized); often with dysphonia, mennonites
DYT7	AD	18p	Unknown	Adult-onset cervical dystonia
DYT8	AD	2q35	PNKD protein (formerly myofibillogenesis regulator)	Paroxysmal nonkinesigenic dyskinesia [Mount-Reback type]
DYT11	AD	7q21.3	Epilsilon sarcoglycan [SGCE]	Myoclonic dystonia; tremors, myoclonus (parkinsonism, alcohol-responsive, juvenile-onset)
DYT12	AD	19.q13.2	Na+/K+-ATPase alpha 3 subunit [ATP1A3]	Rapid-onset dystonia-parkinsonism
DYT17	AR	20p11.2-q13	Unknown	Juvenile-onset torticollis, segmental and generalized spread
DYT18	AD	1p34.2	SLC2A1, glucose transporter 1 [GLUT1]	Paroxysmal exertional dyskinesia [PED]
DYT19	AD	16q13-21	Unknown	Paroxysmal kinesigenic dyskinesia [EKD2] but without epilepsy
DYT20	AD	2q31	Unknown	Paroxysmal nonkinesigenic dyskinesia [PNKD2]
DYT23	AD	9q34.11	CDKN1A-interacting zinc finger protein 1 [CIZ1]	Cervical dystonia
DYT24	AD	11p14.2	Anoctamin 3 [ANO3]	Cervical-brachial-cranial dystonia, jerky torticollis
DYT25	AD	18p11.21	Guanine nucleotide-binding protein alpha-activating [GNAL]	Craniocervical dystonia

AD = autosomal dominant; AR = autosomal recessive.

turn converts tyrosine to levodopa. Inheritance is autosomal dominant with reduced penetrance that appears to be sex-influenced (ie, higher in girls). Although the dystonia may improve dramatically with anticholinergic medications such as trihexyphenidyl, a trial of oral levodopa therapy at low doses (usually no more than 300–400 mg daily) is useful for diagnosis as well as for treatment. Additional support for the diagnosis can be obtained from a phenylalanine-loading test, in which blood levels of phenylalanine remain elevated for a prolonged period, because of the role of tetrahydrobiopterin as a cofactor for phenylalanine hydroxylase as well as tyrosine hydroxylase. Measurement of biopterin metabolites in cerebrospinal fluid may also aid in diagnosis.

In addition to classic DRD due to heterozygous *GCH1* mutations, DRD may result from homozygous or compound heterozygous mutations in *GCH1*, in genes for other enzymes involved in pterin metabolism, and in genes encoding tyrosine hydroxylase. Patients with these defects are often more severely affected clinically, and features due to deficiency of norepinephrine and serotonin may predominate.

Myoclonus-dystonia (DYT11) is a combined dystonia syndrome with prominent myoclonic jerks, usually affecting the arms and trunk more than the legs. Inheritance is autosomal dominant, and many patients have a mutation in the epsilon-sarcoglycan (*SGCE*) gene on chromosome 7q21. Onset is usually in childhood or adolescence. The symptoms characteristically respond to alcohol, and alcoholism (as well as other psychiatric disorders) is not uncommon.

Another rare dystonia combined syndrome is *rapid-onset dystonia-parkinsonism* (DYT 12), in which dystonia

and parkinsonism begin suddenly in adolescence or early adulthood and progress over hours to weeks, after which the symptoms usually stabilize. Inheritance is autosomal dominant and maps to 19q13. The responsible gene codes for the A3 catalytic subunit of the Na^+/K^+-ATPase pump.

Although the causes of combined dystonia are numerous, and increasing, patients with isolated dystonia significantly outnumber the secondary cases. Nevertheless, it is important to identify patients with combined dystonia, as treatment of the underlying condition may be warranted. Factors that raise the likelihood that dystonia is acquired from a specific medical or neurologic cause include history of a potentially etiologic factor (eg, perinatal injury, stroke, encephalitis, head trauma or peripheral trauma, brain tumor, exposure to neurotoxic agents); abnormalities in the neurologic examination (including hemidystonia), neuroimaging, or laboratory evaluation; onset of dystonia at rest rather than action; early onset of cranial dystonia or late onset of leg dystonia; and evidence that the dystonia is psychogenic.

One cause of acquired dystonia is exposure to drugs that block dopamine receptors; neuroleptic agents used in psychiatric practice and the antiemetics are most frequently responsible. Dystonia may occur soon after initiation of therapy (*acute dystonic reaction*) or after prolonged treatment (*tardive dystonia*). These are discussed in more detail in the section on drug-induced movement disorders. Exogenous causes also include injury to the CNS (especially the basal ganglia, cerebellum, and thalamus) or peripheral nervous system; dystonia can be a feature of complex regional pain syndrome. It is also relatively common for dystonia to emerge through psychogenic mechanisms; features that suggest a nonorganic etiology include movements that vary over time, disappearance with distraction, give-way weakness, and sensory findings that do not conform to a physiologically plausible pattern.

Inherited degenerative diseases that can cause dystonia include many autosomal dominant and autosomal recessive conditions, X-linked dominant and recessive conditions, and mitochondrial defects. As mentioned previously, these diseases usually do not cause pure dystonia. *Wilson disease* is an important consideration, because it requires early treatment. It results from mutations in the *ATP7B* gene on chromosome 13, which produce a defect in copper metabolism, leading to the insidious development of neurologic, psychiatric, or hepatic dysfunction. Inheritance is autosomal recessive; more than 200 different mutations have been reported, making genetic testing impractical. When onset is in childhood, Wilson disease usually presents with hepatic dysfunction, but neurologic presentation is most typical in adult-onset disease. Dystonia can be generalized, segmental, or multifocal, but cranial involvement is characteristic; Wilson's original 1912 monograph highlighted the typical "sardonic" smile. Other common neurologic abnormalities include tremor (classically "wing-beating"), dysarthria, dysphagia, drooling, ataxia, and dementia. In addition to brain and liver (cirrhosis, acute hepatitis) involvement, systemic findings can involve the eyes, heart, kidneys, bones, joints, glands, and muscles.

Rarer heredodegenerative causes of dystonia include other autosomal-recessive inborn errors of metabolism, such as Niemann-Pick type C, neuronal ceroid lipofuscinosis, GM1 and GM2 gangliosidoses, glutaric academia, and methylmalonic aciduria. Formerly called *Hallervorden-Spatz disease*, *pantothenate kinase–associated neurodegeneration* (PKAN) is an autosomal recessive disease resulting in abnormal deposition of iron in the basal ganglia, producing childhood onset of dystonia, spasticity, seizures, and dementia. Other inherited causes of dystonia (often accompanied by parkinsonism and other neurologic signs) that are associated with neurodegeneration with brain iron accumulation include PLA2G6 (PARK14)-associated neurodegeneration, neuroferritinopathy, and Kufor-Rakeb disease (PARK9). *Lubag* (DYT3) is an X-linked recessive dystonia-parkinsonism affecting male Filipinos. Usual onset is in adulthood, with cranial or generalized dystonia; parkinsonism may co-occur or develop later. The course tends to be progressive. The *deafness-dystonia (Mohr-Tranebjaerg) syndrome* is an X-linked recessive condition with mutation in the *DDP1* gene. The spinocerebellar ataxias (especially SCA3 [*Machado-Joseph disease*], SCA2, and SCA17) can be associated with dystonia, as can *dentatorubropallidoluysian atrophy*.

Pathoanatomy

Many cases of secondary dystonia are associated with lesions of the basal ganglia (especially the putamen), or with their connections. Degenerative brain changes are not reported in primary dystonia, but relatively few brains have been studied. One study described neuronal inclusions in the brainstem of DYT1 cases. Increased copper deposition in the basal ganglia of adult-onset focal dystonia has been described. Functional imaging of DYT1 patients with PET demonstrates altered metabolism in neural circuits involving the cerebral cortex, basal ganglia, thalamus, and cerebellum.

Prevention

No intervention is known to prevent the development of dystonia. Genetic counseling is useful in educating patients about the likelihood of transmitting the condition to successive generations.

Clinical Findings

A. Laboratory Findings

Like most movement disorders, the diagnosis of dystonia is made on clinical grounds rather than on the basis of laboratory testing. Nevertheless, the cause of the dystonia sometimes can be elucidated through further investigations. The primary and dystonia-plus dystonias for which genetic testing is currently commercially available are DYT1, DYT6, DRD, and myoclonus-dystonia. A positive result obviates the need for further diagnostic testing. Genetic counseling must be available for patients undergoing this test.

Genetic testing for DYT1 dystonia is indicated for patients with onset of dystonia before 26 years of age, as well as for patients with later onset who have a relative with early-onset dystonia. Data to guide DYT6 testing are insufficient at present. Most patients with clinically typical DRD have identified mutations in *GCH1* if comprehensive analysis is performed, including testing for deletions. There is genetic testing for myoclonus-dystonia, although many sporadic cases do not harbor *SGCE* mutations. Genetic testing is also available for many of the secondary dystonias, including SCAs and PKAN. An excellent resource for genetic counseling and testing information is www.genetests.org, a publicly funded resource.

If genetic testing is negative or is not indicated, much of the remaining work-up is directed toward identifying a secondary cause for the patient's dystonia. Treatable conditions that should always be considered in the differential diagnosis include DRD and Wilson disease. We offer a trial of carbidopa/levodopa to all non-DYT1 patients with early onset of symptoms as well as to late-onset patients with features suggesting DRD (ie, parkinsonism, diurnal variation). The dose is increased as tolerated over several weeks; although a daily dose of 600 mg levodopa is sometimes required, failure to respond to a dose of 300 mg/day usually excludes the diagnosis of DRD. Wilson disease should be excluded in patients with onset of dystonia before age 50. Diagnostic laboratory findings in patients with neurologic signs due to Wilson disease include MRI abnormalities involving the putamen, thalamus, and brainstem; reduced serum ceruloplasmin; increased 24-hour urinary copper excretion; and Kayser-Fleischer rings in the cornea due to deposition of copper in Descemet membrane. These are best seen with slit lamp examination. Although noninvasive studies are usually adequate for diagnosing neurologic Wilson disease, liver biopsy to assess copper content has high sensitivity and may be considered.

Evaluation of secondary dystonia is dictated by clues provided by the history and examination. Routine blood tests such as complete blood count, electrolytes, glucose, calcium, magnesium, coagulation profile, and kidney, liver, and thyroid function may be supplemented by sedimentation rate, antinuclear antibody screen, and syphilis screen. Specific clinical findings or laboratory abnormalities may dictate further investigations, including electrophysiologic studies, lumbar puncture, biopsy of various tissues, or metabolic studies of blood, urine, or cerebrospinal fluid. Testing for the human immunodeficiency virus should be considered in the appropriate setting.

B. Imaging Studies

All patients suspected of having a secondary form of dystonia should undergo MRI (or, if not possible, CT) of the brain. In primary dystonia and in the dystonia-plus syndromes, brain MRI is normal. In secondary and heredodegenerative dystonias, MRI may show calcification, necrosis, or other abnormalities in the basal ganglia. In some cases, these changes are quite specific; for instance, T2-weighted MRI in PKAN often shows hypointensity in the globus pallidus with medial hyperintensity (the "eye-of-the-tiger sign"). PET scanning may be supportive of primary dystonia, but rarely is crucial in making the diagnosis.

Differential Diagnosis

A variety of central and peripheral nervous systems disorders, as well as non-neurologic conditions, can be associated with abnormal postures that resemble torsion dystonia (sometimes called *pseudodystonia*). For example, tonic seizure activity can produce sustained twisting movements. Head tilt can reflect palsy of the trochlear nerve, vestibulopathy, pathology in the posterior fossa, or a retropharyngeal soft tissue mass. *Stiff person syndrome* causes contraction of axial and proximal limb muscles. Nerve and muscle abnormalities include *neuromyotonia (Isaac syndrome)*, the myotonic disorders, inflammatory myopathies, and glycogen storage diseases (eg, *Satoyoshi disease*). Carpopedal spasms of *tetany* can be the manifestation of hypocalcemia, hypomagnesemia, or alkalosis. Orthopedic and rheumatologic processes involving bones, ligaments, or joints can result in abnormal postures. In *Sandifer syndrome*, patients (typically young boys) with hiatal hernia develop head tilt in association with gastroesophageal reflux.

Complications

Long-standing torsion dystonia can result in fixed contractures or scoliosis. Dystonic storm or status dystonicus is a rare but life-threatening disorder that may occur in primary or secondary dystonia, especially in children or adolescents with underlying generalized dystonia. Severe repeated dystonic spasms may interfere with respirations and cause hyperpyrexia, dehydration, and acute renal failure secondary to rhabdomyolysis; it requires aggressive treatment that may include emergent deep brain stimulation.

Treatment

When dystonia is secondary, treatment of the underlying condition may produce improvement in the dystonia. In patients with tardive dystonia or an acute dystonic reaction, dopamine receptor–blocking drugs should be eliminated or replaced whenever possible (as detailed in section on drug-induced movement disorders). Structural lesions may be amenable to surgical correction. Management of Wilson disease consists of copper chelation therapy (usually with penicillamine as a first-line agent) and oral zinc, which induces copper-binding metallothionein in enterocytes. Some of the inborn errors of metabolism may respond to dietary restriction or supplementation. Patients with DRD usually are maintained on low-dose carbidopa/levodopa therapy. Although currently there is no curative therapy for primary dystonia, several effective options for symptomatic treatment are available; these include oral pharmacologic agents, chemodenervation, and surgery. Of the various oral medications that have been studied, anticholinergic agents are the most efficacious

Table 15–13. Oral medications used in management of dystonia.

	Usual Effective Dose (mg/day)
Anticholinergic agents	
Trihexyphenidyl	6–80
Benztropine	4–8
Ethopropazine[a]	100–400
Benzodiazepines	
Clonazepam	1–4
Diazepam	10–60
Lorazepam	1–6
Dopamine-depleting agents	
Tetrabenazine	50–200
Reserpine	1–3
GABA agonist	
Baclofen	30–80

GABA = γ-amino butyric acid.
[a]Not available in the United States.

(Table 15–13). Trihexyphenidyl is the best studied and probably the most widely used, although benztropine, diphenhydramine, and ethopropazine (which is not available in the United States) may be useful as well. Use is often limited by peripheral anticholinergic adverse effects, including blurred vision, dry mouth, urinary retention, sedation, and confusion, and doses should be titrated slowly. Pilocarpine eye drops or oral pyridostigmine, a peripherally acting anticholinesterase, may be effective in counteracting these unwanted effects. Anticholinergic medications can be used singly or in combination with other drugs, including baclofen, benzodiazepines, and muscle relaxants such as cyclobenzaprine. Dopamine-depleting agents and atypical antipsychotics may be helpful in the treatment of dystonia. Preliminary observations suggest that newer antiepileptic drugs (eg, zonisamide, topiramate, levetiracetam) may be useful in suppressing dystonic movements, but further study of their role is needed.

Chemodenervation of overactive muscles by injection of botulinum toxin is the treatment of choice for focal dystonia. The toxin produces muscle weakness by interfering with proteins in the presynaptic nerve terminal that are responsible for release of acetylcholine into the neuromuscular junction. This therapy is effective in the treatment of blepharospasm, cervical dystonia, spasmodic dysphonia, writer's cramp, and oromandibular dystonia. Side effects can arise from unintended weakness in nearby muscles due to diffusion of toxin. Antibodies to botulinum toxin can develop with repeated injections, resulting in loss of therapeutic effect.

Patients whose dystonia is disabling and refractory to oral medications and chemodenervation may be candidates for surgery of the peripheral or CNS. Thalamotomy, pioneered in the 1960s, is the oldest CNS surgical approach to dystonia. Based on the efficacy of pallidotomy for treating dyskinesias and dystonia in Parkinson disease and neurophysiologic studies that demonstrate an abnormal pattern of neuronal discharging from the globus pallidus in patients with generalized dystonia, current surgical interventions target this region of the basal ganglia. Although either pallidotomy or DBS can modulate the pallidal output, DBS has the advantages over ablative surgery of being reversible and having multiple stimulator parameters that can be adjusted noninvasively to optimize the outcome in a particular patient. DBS has been performed in patients with primary generalized dystonia, secondary generalized dystonia, cervical dystonia, blepharospasm, Meige syndrome, and tardive dystonia. In a 2006 meta-analysis of 24 studies including 137 patients who underwent DBS for dystonia, the greatest improvement was seen in patients with PKAN, DYT1 dystonia, and tardive dystonia. Surgical denervation procedures such as ramisectomy and rhizotomy as well as myectomy may be useful in selected cases of cervical dystonia.

Because patients with dystonia often have associated comorbidities, consultation with specialists including orthopedic surgeons, physiatrists, and psychiatrists can be useful. Many patients derive benefit from physical, occupational, and speech therapy. Various devices have been developed that provide sensory input via the affected body part, simulating a sensory trick. Alternative and complementary modalities such as acupuncture, biofeedback, massage, and relaxation techniques may be helpful.

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MYOCLONUS

ESSENTIALS OF DIAGNOSIS

- Brief, sudden, shock-like, involuntary muscle contractions

General Considerations

Myoclonus means "a quick movement of muscle." Myoclonic jerks are shock-like, involuntary muscle contractions that may be rhythmic and repetitive or random and unpredictable. The jerks may be focal, segmental, or generalized. Myoclonic jerks are often stimulus-sensitive and induced by sudden noise or movement. Positive myoclonus, a sudden,

brief muscle jerk, is caused by active muscle contraction. Negative myoclonus (ie, asterixis) is a sudden, brief, cessation of muscle contraction in actively contracting muscles that results in loss of posture followed by a compensatory contraction. Myoclonus may be difficult to distinguish from other hyperkinetic involuntary movements, especially tics and tremor. Unlike tics, myoclonus cannot be suppressed, and it does not wax and wane. In addition, myoclonus usually produces a faster movement than a tic. Tremor is usually slower than myoclonus and is rhythmic and oscillatory.

Classification

Etiologic classification of myoclonus includes physiologic, essential, epileptic, and symptomatic forms. Normally occurring muscle jerks such as hiccups (myoclonus of the diaphragm) and hypnic jerks are termed *physiologic myoclonus. Essential myoclonus* is a rare disorder that may be hereditary (autosomal dominant), sporadic, or of unknown cause. An important inherited cause of myoclonus that usually starts in childhood and is commonly accompanied by dystonia is myoclonus-dystonia due to mutations in epsilon–sarcoglycan (DYT11); the syndrome is discussed earlier in the section on dystonia. Myoclonus that occurs in the setting of underlying epilepsy is termed *epileptic myoclonus.* Examples include epilepsia partialis continua and juvenile myoclonic epilepsy. Progressive myoclonic epilepsy includes a group of degenerative disorders characterized by epilepsy, myoclonus, and progressive neurologic deterioration. Examples of progressive myoclonic epilepsies include neuronal ceroid lipofuscinosis, Lafora body disease, Unverricht-Lundborg disease, myoclonus with epilepsy and ragged-red fibers (MERFF), and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). *Symptomatic myoclonus* may occur in the setting of renal and liver failure, drug intoxication, anoxic brain injury (posthypoxic myoclonus), Creutzfeldt-Jakob disease, Huntington disease, Alzheimer disease, and parkinsonism.

Myoclonus may originate from the cerebral cortex, subcortical structures, brainstem, spinal cord, or peripheral nerves. Choice of antimyoclonic therapy is guided by the origin of the myoclonus. Definitive localization of the focus of myoclonus requires complex electrophysiologic studies that are not routinely available.

Clinical Findings

A. Symptoms and Signs

Cortical myoclonus manifests as stimulus-sensitive, spontaneous, arrhythmic muscle jerks, often restricted to a body part such as the arm, leg, or face. Cortical myoclonic jerks originate within the sensorimotor cortex and may be manifestations of a focal cortical lesion (tumor, stroke, inflammation), focal epilepsy, or epilepsia partialis continua. Subcortical myoclonus most often originates from the brainstem, resulting in stimulus-sensitive, generalized jerks. Subcortical myoclonus may occur in primary generalized epilepsy, multiple sclerosis, encephalitis, Creutzfeldt-Jakob disease, Alzheimer disease, degenerative disease, toxic states, and metabolic encephalopathies. Two types of myoclonus originate from the spinal cord. Spinal segmental myoclonus is typically rhythmic, stimulus-sensitive, and restricted to a few adjacent segments of the spinal cord. Propriospinal myoclonus causes slow, generalized truncal jerks that produce truncal flexion, and in a subset of patients the etiology is psychogenic. Myoclonus can result from a peripheral nerve lesion. Movements are limited to the involved motor unit, usually are not sensitive to stimuli, and are irregular. An example is hemifacial spasm caused by a lesion to the facial nerve.

B. Imaging Studies and Other Tests

Electroencephalography (EEG) may be useful to clarify an epileptic syndrome, but cortical myoclonus does not produce abnormalities on routine EEG. Definitive localization of a cortical myoclonic focus requires time-locked, back-averaged EEG, a highly specialized technique. In cortical myoclonus, somatosensory evoked potentials may show large-amplitude potentials. CT or MRI may reveal a focal, causal lesion.

Treatment

Therapy of myoclonus is empiric, and for best results, antimyoclonic agents are used in combination (Table 15–14). Choice of therapeutic agents is based on diagnosis, origin of

Table 15–14. Treatment of myoclonus.

Drug	Initial Adult Dose	Usual Effective Dose	Indication
Clonazepam	0.5 mg/day	2 mg/day divided 3 times a day	Posthypoxic myoclonus Spinal myoclonus Progressive myoclonic epilepsy Essential myoclonus
Levetiracetam	250 mg/day	1000–1500 mg/day	Posthypoxic myoclonus Cortical myoclonus Spinal myoclonus
Piracetam	400 mg 3 times a day	1200–16,000 mg/day divided 3 times a day	Posthypoxic myoclonus Cortical myoclonus Progressive myoclonic epilepsy Essential myoclonus
Primidone[a]	25 mg/day	500–750 mg/day	Cortical myoclonus
Valproate	125 mg 2 times a day	750–1000 mg/day divided 2 times a day	Most forms of myoclonus

[a]Not approved by the Food and Drug Administration.

myoclonus, and side-effect profile. Standard antimyoclonic drugs include clonazepam, levetiracetam, piracetam, primidone, and valproic acid. Valproic acid is effective in both cortical and subcortical myoclonus. Levodopa-carbidopa and sodium oxybate have been reported to benefit myoclonus dystonia, and the latter also may help posthypoxic cortical myoclonus.

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TOURETTE SYNDROME & TIC DISORDERS

ESSENTIALS OF DIAGNOSIS

- Chronic disorder of motor and vocal tics, usually beginning before the age of 21
- Male predominance
- Frequently familial
- Frequently associated with attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD)

General Considerations

Tic disorders are conditions that cause sudden, repetitive, stereotyped, purposeless brief actions, gestures, sounds, and words. The prototype tic disorder, Tourette syndrome (TS), was described in a seminal 1885 report by George Gilles de la Tourette, in which several cardinal observations were made: onset during childhood, the hereditary nature of the condition, male predominance, and association with psychiatric disease.

TS is worldwide in distribution, with a 3:1 male gender preponderance. Estimates of the prevalence of TS in the population vary markedly, ranging as high as 4.2%, depending on the methodology of the study. The prevalence of all types of tic disorders is considerably higher, in the range of 20%. Studies of schoolchildren with learning difficulties tend to show a higher prevalence of TS. Tic disorders may exist in pure form, but they are often associated with comorbid psychiatric symptoms, as described later.

Despite the overwhelming clinical evidence that most cases of tic disorder are familial, no gene for TS has been identified. The cause of tics is unknown, but the leading hypothesis postulates a heightened sensitivity of dopamine receptors in the caudate and putamen, termed the *dopamine hypersensitivity hypothesis*. This notion is supported by the clinical observation that tics occur in many disorders of the basal ganglia, including Parkinson disease and Huntington disease. In addition, dopamine receptor–blocking agents suppress tics.

Clinical Findings

A. Tic Phenomenology

Tics are abrupt, purposeless, brief movements that occur suddenly out of a background of normal motor activity. Tics can be *simple* or *complex*. Simple motor tics are quick and short-lived: blinking, ocular deviation, facial grimacing, neck movements, and shoulder shrugging are examples of simple motor tics. Some simple motor tics are slower, sustained, tonic movements, such as limb muscle tensing or abdominal tightening. Other tics have a torsional, twisting aspect that is sustained at the peak of contraction, resembling dystonia.

Complex tics are coordinated, sequenced stereotyped acts, such as tapping or touching, or pantomiming an obscene gesture (copropraxia). Complex tics may have the appearance of compulsive acts, and indeed, the distinction is not always clear. Compulsions are driven by an irrational fear or anxiety that can be allayed by performing a specific sequence of gestures or actions, such as tapping a certain number of times.

The term *stereotypy* or *stereotyped movement* describes continuous and repetitive tic movement of restricted repertoire. Usage has linked stereotypy with developmental delay, autism spectrum disorder, and other neurobehavioral disorders—but in appearance, stereotypies resemble tics.

Simple vocal or phonic tics include throat-clearing noises, grunting, clicking, sniffing, barking, squeaking, and other purposeless sounds. Verbal tics, consisting of repetitive purposeless words and phrases, including obscenities (coprolalia), are example of complex vocal tics.

Most patients with tics report a premonitory sensation or urge, coincident with a build-up of inner tension that is relieved temporarily when the tic is released. Sometimes patients describe their prodromal feeling as a localized sensation, such as a tingling or burning, in the body part that participates in the tic. Many individuals can temporarily suppress their tics, especially during intense situations such as an interview or a visit to the physician, only to experience an amplified release of tics after the encounter. It is commonly observed that tics may decrease during times of intense concentration, such as when playing a videogame or participating in sports. Tics may also persist during sleep. Echo phenomena are common in TS: Some individuals can imitate with extraordinary speed and accuracy a sound (echolalia) or gesture (echopraxia). A related phenomenon is the tendency for some patients to repeat their own stereotyped phrases, words, and syllables, termed *palilalia*.

B. Clinical Features of Tic Disorders

Tic disorders usually begin in childhood. The mean age at onset is about 6 years, with increasing severity over the first several years. In 96% of patients, the tics present before

age 11. The most common initial symptom is eye blinking, and during the course of the disorder, nearly all patients experience tics involving the face and neck. Vocalizations are reported as the initial symptom in about one third of patients, and the most common phonic tic is throat-clearing. Sniffing and coughing are frequent phonic tics that can be quite disruptive and trigger an initial medical evaluation for asthma or an otolaryngeal problem. Coprolalia, the most notorious and potentially disabling of tics, is present only in a small minority of patients with tic disorders, estimated at less than 3%.

About 50% of TS patients demonstrate symptoms of OCD, such as compulsive checking, counting, obsessive orderliness, hoarding, and obsessive fears or worries. About half of patients with TS show evidence of ADHD, manifested by inattention, distractibility, impulsivity, and hyperactivity, or pure attention deficit disorder without hyperactivity (ADD). Boys with TS are more likely to have ADHD symptoms, whereas girls with TS have OCD symptoms. In contrast to tics, ADHD and OCD symptoms are significantly associated with impaired emotional and social adjustment. A small number of individuals manifest self-injurious behavior. In addition to ADHD and OCD, the behavioral spectrum of TS includes conditions such as generalized anxiety disorder, panic attacks, phobias, and mood disorder. Overall, patients with TS have normal intelligence.

C. Classification of Tic Disorders

The spectrum of tic disorders ranges from mild, transient tics to multiple, chronic, disabling tics with associated psychopathology. For the purpose of diagnostic clarity, classification systems have evolved using standard clinical criteria. Primary tic disorders are "essential" idiopathic conditions in which the tics represent the only neurologic sign.

Secondary tic disorders are neurologic disorders in which tics are part of a larger neurologic syndrome that may include developmental delay, parkinsonism, dystonia, chorea, or a known genetic or acquired neurologic injury, including trauma, infection, or stroke. Secondary tic disorders almost always result from lesions of the basal ganglia. Among the many neurodegenerative causes of tic disorders are Huntington disease, neuroacanthocytosis, and Parkinson disease. The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal infections, or PANDAS, is a concept of some controversy suggesting that a large number of cases of tic disorders and obsessive-compulsive behaviors result from an immune-mediated cross-reaction between streptococcal infection and the basal ganglia. The strength of the association is weak, however, and does not justify the treatment of routine TS with antibiotics or immune-modulating therapy, such as plasmapheresis or intravenous immune globulin.

The classification criteria for primary tic disorders, formulated by the Tourette Syndrome Classification Study Group in 1993, are listed in Table 15–15. The most common and mildest tic disorder is transient tic disorder (TTD), estimated to occur in up to 24% of schoolchildren. The disorder is characterized by tics that go into permanent remission within 1 year of onset, and so the diagnosis can only be made retrospectively. Chronic multiple tic disorder (CMTD) is a syndrome of multiple motor or vocal tics, but not both. Chronic single tic disorder (CSTD) is a condition in which patients experience only a single, recurrent motor or vocal tic. Such a classification is artificial, because all tic disorders represent variants that share a common underlying pathophysiology and genetic predisposition. The severity of a tic disorder is independent of the temporal profile, because a patient with a single, disruptive tic may be more disabled than an individual with multiple mild tics.

Table 15–15. Primary tic disorders.

Diagnosis	Criteria
Tourette syndrome	Presence of multiple motor and vocal tics Age at onset <21 y Tics must occur many times daily, nearly every day, over a period of >1 y Disturbance causes marked distress or significant impairment in daily functioning Condition cannot be ascribed to known neurologic disorder (symptomatic or secondary tic disorder)
Transient tic disorder	Duration of tic disorder <1 y
Chronic tic disorder	Chronic motor *or* chronic vocal tics (*but not both*) >1 y
Chronic single tic disorder	Chronic single motor *or* chronic single vocal tic
Adult-onset tic disorder	Tic disorder that begins after the age of 21 y Two temporal patterns: de novo adult-onset tics and *recurrent* childhood tics: a tic disorder that went into remission and recurred during adulthood

Differential Diagnosis

Tics can usually be differentiated from other major types of hyperkinetic movements because they are uniquely stereotyped and usually preceded by a premonitory sensation. A blinking tic may have the appearance of blepharospasm, but the presence of tics at other body sites marks the condition as a tic disorder. Furthermore, although tics typically begin in childhood, blepharospasm is largely a disorder with onset in adult life. Complex motor tics may be difficult to differentiate from compulsions, and indeed many patients exhibit both types of behaviors. Tics occur automatically, with little premeditation, whereas compulsive motor acts are deliberately performed, purposeless actions often driven by

an obsessive idea and may be repeated a specified number of times in a certain order.

Treatment

A. General Approach

The first step in the management of TS is to determine whether treatment is even required. The goal of treatment is not to achieve complete tic suppression but to allow a patient to function and live normally. It is always important to consider the treatment of tics in the context of the associated psychopathology (ADHD, ADD, OCD, anxiety, depression, personality disorder), which, if present, can be more disabling than the tic disorder. Furthermore, it is critically important to target the most distressing or disabling feature in the treatment plan. A comprehensive approach involves psychiatric evaluation and treatment, education of patients, family members, and school personnel, restructuring the school environment, and supportive counseling. In recent years, there has been increasing emphasis on behavioral modification techniques for controlling tics, although further study is needed.

B. Pharmacotherapy

Medication therapy should be considered only if the symptoms of TS are functionally disabling and not remediable by nonpharmacologic interventions. A number of therapeutic agents are available to treat the symptoms of TS, and each medication should be chosen on the basis of specific target symptoms and potential side effects. For example, tic suppression may be the most important goal for one patient, whereas treatment of OCD may take precedence in another.

The choice of medication depends on the severity of symptoms, side-effect profile, presence of comorbid psychopathology, and the physician's experience. For controlling tics, centrally acting α-2 agonists, such as clonidine or guanfacine, are considered drugs of first choice because of a favorable side-effect profile. Clonazepam may be helpful in the treatment of tics and is well-tolerated in children. Medications that reduce or blunt dopaminergic transmission predictably suppress tics, but they carry a higher risk of adverse effects. The catecholamine-depleting agents tetrabenazine and reserpine are effective tic-suppressing agents, but they may cause hypotension, depression, sedation, and reversible parkinsonism.

Neuroleptic drugs (haloperidol, risperidone, trifluoperazine, molindone, thiothixene, olanzapine, ziprasidone, pimozide, and most recently aripiprazole), which act as dopamine receptor antagonists, are the most predictably effective tic-suppressing medications but cause weight gain, depression, sedation, and they also carry a small but definite risk of inducing permanent tardive dyskinesia. Risperidone has been shown in a number of studies to reduce tic frequency and intensity. Only haloperidol and pimozide have actually been approved by the FDA for the treatment of TS. The list of incompletely evaluated agents for treating tics is long and includes the dopamine agonist ropinirole and nicotine. Patients with focal tics restricted to a small body part, such as blinking tics or a stereotyped neck twitch, may be treated successfully using injections of botulinum toxin.

Patients with associated ADHD or OCD may require specific treatment, because drugs used for tic suppression do not help these behaviors. ADHD symptoms are treated using psychostimulants, and OCD symptoms are treated using serotonin reuptake inhibitors. Although many patients with tic disorders are followed by pediatricians or primary neurologists, a psychiatrist may be required to prescribe and supervise the required pharmacotherapy. The pharmacologic treatment of TS is summarized in Table 15–16. Many of the agents in common use are not approved for this indication, and caution must be exercised to avoid adverse effects and medication interactions. The dose ranges for each agent are provided, but it is important for clinicians to tailor treatment to the individual and seek the advice of specialists, including psychiatrists, in complex cases.

Prognosis

The course of tic disorders is unpredictable, marked by tic patterns that evolve, wax, and wane, varying in severity and prevalence over time. The treatment of tic disorders is purely symptomatic, and there is no evidence that it has any effect

Table 15–16. Agents for treating tic disorders.

Drug	Usual Effective Dose (mg/day)	Potential Adverse Effects
Clonidine	0.05–0.5	Drowsiness, hypotension
Guanfacine	0.5–4	Drowsiness, hypotension
Clonazepam	0.25–2	Drowsiness, irritability
Tetrabenazine	12.5–100	Drowsiness, hypotension, depression, parkinsonism
Reserpine	0.25–3	Drowsiness, hypotension, depression, parkinsonism
Risperidone	0.5–12	Parkinsonism, weight gain, risk of tardive dyskinesias
Olanzapine	2.5–15	Parkinsonism, risk of tardive dyskinesias
Pimozide	0.5–10	Parkinsonism, risk of tardive dyskinesias, retinopathy, prolonged QT interval
Fluphenazine	1–5	Parkinsonism, risk of tardive dyskinesias
Haloperidol	0.5–20	Parkinsonism, risk of tardive dyskinesias

on the long-term course of the condition. Approximately one half of patients experience a gradual and complete remission in tics by the end of adolescence. Tic severity during childhood does not appear to predict the long-term outcome. In general, the prognosis for normal occupational and social functioning depends more on the associated psychopathology than the tics.

Frundt O, Woods D, Ganos C. Behavioral therapy for Tourette syndrome and chronic tic disorders. *Neurol Clin Pract* 2017;7(2):148–156. [PMID: 29185535]

Piacentini J, et al. Behavior therapy for children with Tourette disorder: Randomized controlled trial. *JAMA* 2010;303:1929–1937. [PMID: 20483969] (A controlled trial of behavioral therapy shows improvements in tic severity using the Yale Global Tic Severity Scale.)

Quezada J, Coffman KA. Current approaches and new developments in the pharmacological management of Tourette syndrome. *CNS Drugs*. 2018;32(1):33–45. [PMID: 29335879]

The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: A randomized controlled trial. *Neurology* 2002;58:527–536. [PMID: 11865128] (Clinical trial describing treatment of Tourette syndrome and ADHD concludes that methylphenidate can help behavioral symptoms without exacerbating tics.)

TARDIVE DYSKINESIA & OTHER DRUG-RELATED MOVEMENT DISORDERS

ESSENTIALS OF DIAGNOSIS

- Dopamine receptor–blocking agents (DRBAs) may cause acute, subacute, and chronic, persistent hyperkinetic movement disorders
- Acute dystonia and akathisia are self-limited movement disorders that are triggered by exposure to high-potency DRBAs
- Tardive dyskinesias are a group of iatrogenic, persistent movement disorders induced by chronic exposure to DRBAs and include classic tardive dyskinesias, tardive dystonia, and tardive akathisia
- Tardive syndromes have a low spontaneous remission rate
- Drug-induced parkinsonism is a dose-dependent, reversible syndrome caused by DRBAs

General Considerations

Many drugs cause abnormal movements. Of particular note are movement disorders resulting from exposure to neuroleptics and other agents that block central dopamine receptors. These neurologic syndromes may be acute and self-limited or chronic, persistent, and irreversible. The range of abnormal movements caused by DRBAs is wide, and it is important for clinicians to recognize the individual drug-induced syndromes because (1) *acute* drug reactions are immediately treatable if recognized and (2) the appearance, or phenomenology, of the abnormal movements comprising a *tardive* syndrome determines treatment and prognosis. Because drug-induced movement disorders are iatrogenic, and sometimes permanent, it is essential that clinicians warn patients about their potential to occur when prescribing these medications.

The entire category of movement syndromes caused by DRBAs is sometimes conflated as "extrapyramidal syndrome" (EPS), but the term vastly oversimplifies a complex group of disorders, each with its own distinct clinical features, therapeutic approach, and prognosis. Tardive movement disorders tend to appear late in the course of treatment, hence the term *tardive*. DRBAs may also cause *acute* movement disorders, chiefly acute dystonia and acute akathisia. In addition, chronic exposure to DRBAs may produce reversible parkinsonism.

Most DRBAs are neuroleptics used for the treatment of psychosis, and although many newer agents are marketed as "atypical," such as risperidone, these drugs can readily induce parkinsonism and tardive dyskinesias. To date, all of the newest DRBAs, including lurasidone, aripiprazole, ziprasidone, paliperidone, among other recently developed agents, have been reported to cause parkinsonism or tardive dyskinesias. In addition, many other agents used for depression (amoxapine), gastrointestinal ailments (metoclopramide), and cardiac disease (flunarizine) are DRBAs with the potential to cause tardive syndromes (Tables 15–17 and 15–18).

The risk of developing a tardive syndrome is related to the avidity of D_2 receptor binding and blockade but presumably also to individual susceptibility factors that have not been elucidated. The only antipsychotic agents that appear to have little or no risk of inducing a tardive syndrome are (1) clozapine and quetiapine, which have weak affinity for D_2 receptors and appear to exert their antipsychotic effects

Table 15–17. Neurologic adverse effects of dopamine receptor antagonists.

Acute reactions
• Acute dystonia
• Acute (or subacute) akathisia
Drug-induced parkinsonism
Neuroleptic malignant syndrome
Tardive syndromes
• Classical tardive dyskinesia
• Tardive dystonia
• Tardive akathisia

Table 15–18. Dopamine receptor–blocking agents.

Class	Drug
Phenothiazines • Aliphatic • Piperidine • Piperazine	Chlorpromazine, triflupromazine Thioridazine, mesoridazine Trifluoperazine, prochlorperazine, perphenazine, fluphenazine
Thioxanthenes • Aliphatic • Piperazine	 Chlorprothixene Thiothixene
Butyrophenones	Haloperidol, droperidol
Diphenylbutylpiperidine	Pimozide
Dibenzazepine	Loxapine
Dibenzodiazepine	Clozapine, quetiapine
Thienobenzodiazepine	Olanzapine
Substituted benzamide	Metoclopramide, tiapride, sulpiride, clebopride, remoxipride, veralipride
Indolone	Molindone
Pyrimidinone	Risperidone
Benzisothiazole	Ziprasidone
Benzisoxazole	Iloperidone
Quinolinone	Aripiprazole
Tricyclic	Amoxapine
Calcium channel blocker	Flunarizine, cinnarizine

Adapted with permission from Fahn S, Jankovic J: *Principles and Practice of Movement Disorders*. Philadelphia, PA: Churchill Livingstone/Elsevier; 2007.

through serotoninergic mechanisms, and (2) pimavanserin, indicated for treating psychosis in PD, which exerts inverse agonist and antagonist activity at serotonin 2A receptors (5-HT_{2A}) receptors.

ACUTE SYNDROMES CAUSED BY NEUROLEPTICS

ESSENTIALS OF DIAGNOSIS

- Acute dystonia is a focal or segmental torsional muscle spasms that usually occurs within hours of treatment using a high-potency dopamine receptor–blocking drug
- Acute akathisia is a sensation of restlessness that occurs within hours of treatment using a high-potency dopamine receptor–blocking drug

1. Acute Dystonia

Clinical Findings

The acute dystonic reaction is a sustained, torsional muscle contraction, usually confined to a body segment, occurring after initial treatment using a DRBA. The classic clinical scenario is that of a young patient who receives a high-potency neuroleptic, such as haloperidol, in the emergency department and subsequently develops a sustained contraction of the neck muscles. All agents that block dopamine D_2 receptors can induce acute dystonic reactions, including risperidone and other so-called "atypical" agents. Serotoninergic agents have also been reported to induce acute dystonic reactions. The onset of symptoms ranges from immediately after the first dose to several days of treatment. In about half of the cases, the acute dystonic reaction occurs within 48 hours, and in 90% by 5 days after starting the therapy.

Acute dystonic reactions most often affect the ocular muscles (oculogyric crisis), face, jaw, tongue, neck and trunk, and less often limbs. A typical acute dystonic reaction may consist of head tilt backward or sideways with tongue protrusion and forced opening of the mouth, often with arching of trunk and ocular deviation upward or laterally. Rarely, the syndrome can recur with subsequent exposures to D_2 receptor–blocking agents.

Treatment

In patients with acute dystonic reactions, symptoms can be relieved within minutes using parenteral anticholinergics or antihistaminics. Diphenhydramine 50 mg or benztropine mesylate 1 to 2 mg or biperiden 1 to 2 mg is given intravenously and can be repeated if the dystonia does not abate within 30 minutes. Intravenous diazepam is also effective and can be used as an alternative therapy. If untreated, the majority of cases resolve spontaneously within 12 to 48 hours after the last dose of the offending agent. DRBAs with high anticholinergic activity have a relatively low incidence rate of acute dystonic reactions, and therefore prophylactic use of anticholinergics (eg, benztropine) has been especially recommended in young patients beginning treatment with high-potency DRBAs.

2. Acute Akathisia

Clinical Findings

Akathisia comprises two elements, one subjective and the other objective. The subjective symptom is extreme restlessness and intolerance of remaining still. Patients complain of a disturbing inner tension with vivid phrases like "I feel that I'm jumping out of my skin" or "I'm about to explode."

The objective component, visible to an observer, are repetitive movements of limited repertoire performed by the patient to relieve the inner restlessness, such as marching in place, shifting the limbs, writhing and rolling movements, or stereotypic caressing or rocking movements. Some patients moan as part of a generalized akathisic state. Most cases of acute akathisia occur within 1 month of drug exposure, or shortly after an increase in the dose of their neuroleptic. Akathisia may occur in any condition of dopamine deficiency or blockade. It was first observed in patients with advanced parkinsonism but is now most frequently encountered as an acute side effect of neuroleptic drugs.

Differential Diagnosis

The differential diagnosis of repetitive movements includes states of agitation due to encephalopathy; pain; or psychiatric disease such as agitated depression, psychosis, or obsessive-compulsive disorder. Unusual syndromes of inner vibrations and tremors are described in patients with parkinsonism, dementia, or tardive dyskinesia.

Treatment

Acute akathisia is self-limited, disappearing on discontinuation of the offending neuroleptic. Acute akathisia can be controlled by anticholinergics when neuroleptics need to be continued; other agents that can reduce akathisia include β-blockers, clonidine, and mirtazapine.

NEUROLEPTIC-INDUCED PARKINSONISM

ESSENTIALS OF DIAGNOSIS

- Dose-dependent parkinsonism caused by DRBAs
- The syndrome may be clinically indistinguishable from classic PD
- Parkinsonism gradually resolves if the offending agent is removed

Neuroleptic-induced parkinsonism is a dose-related side effect of DRBAs and may be indistinguishable in appearance from idiopathic PD. It develops with use of either DRBAs or dopamine-depleting drugs such as reserpine and tetrabenazine. All neuroleptics can induce parkinsonism in proportion to their D_2 receptor affinity, the dosage, and duration of treatment, with the exception of clozapine and quetiapine; other agents that can induce mild reversible parkinsonism include valproate and calcium channel blockers. The incidence of drug-induced parkinsonism in patients taking DRBAs varies from 15% to 60%. Women are almost twice as frequently affected as men, a reverse of the ratio in idiopathic PD. Neuroleptic-induced parkinsonism also occurs increasingly with advanced age, in parallel with the incidence of idiopathic PD.

Drug-induced parkinsonism is typically reversible when the medication is reduced or discontinued, but sometimes the remission of symptoms takes many months. When parkinsonism develops in a patient receiving neuroleptics, the adverse effect should be weighed against the benefits of treatment. If a patient has strong need for DRBA therapy, some degree of parkinsonism may be tolerable. For patients at risk for falling due to drug-induced parkinsonism, a change in therapy should be considered, either reducing the dose of neuroleptic or replacing the DRBA with quetiapine, pimavanserin or clozapine. There is little evidence that dopamine agonists or levodopa ameliorate drug-induced parkinsonism in the presence of a DRBA. Some patients show persisting parkinsonism despite prolonged discontinuation of neuroleptics, probably reflecting the development of actual PD; no pathologically proven case of tardive parkinsonism exists.

TARDIVE SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Tardive dyskinesia is a syndrome of stereotyped, choreic movements involving the face and distal extremities caused by chronic exposure to DRBAs
- Tardive dystonia should be distinguished from classical tardive dyskinesias because it consists of sustained, torsional, often disabling muscle spasms that affect any part of the body
- Tardive akathisia is a syndrome of chronic restlessness resulting from exposure to dopamine receptor–blocking drugs
- Tardive syndromes have a low rate of spontaneous remission and often cause permanent disability

General Considerations

Tardive syndromes are late, persistent abnormal movements induced by chronic exposure to DRBAs. The risk of developing a tardive syndrome is proportional to its dopamine D_2 receptor affinity and the duration of drug exposure, although some cases have appeared within weeks of the first doses. The three main tardive syndromes are (1) classical tardive dyskinesia, (2) tardive dystonia, and (3) tardive akathisia. Tardive dyskinesias are hypothesized to result from permanent alterations in synaptic dopaminergic sensitivity induced by dopamine receptor blockade.

When a tardive syndrome develops, gradual withdrawal of the offending agent should be considered. Abrupt withdrawal of the inciting agent is associated with a more severe emergence of abnormal movements. General treatment guidelines

Table 15–19. General guidelines for treating tardive syndromes.

- Taper and slowly eliminate causative agents, if clinically possible. Avoid sudden cessation of these drugs, which may exacerbate symptoms.
- If it is necessary to treat the movements, the drugs of first choice are the dopamine-depleting drugs reserpine, tetrabenazine, and α-methylparatyrosine. It is important to monitor the development of depression, hypotension, sedation, and parkinsonism.
- If dopamine-depleting agents do not help, consider a trial of clozapine or quetiapine.
- Dopamine receptor–blocking agents may be used as medications of last resort for tardive syndromes, despite the risk of worsening the syndrome over the long term.
- Globus pallidus stimulation should be considered for disabling tardive dystonia if medication treatment fails.

for tardive syndromes are provided in Table 15–19. The remission rate for tardive syndromes is unknown, and permanent symptoms may occur.

1. Classical Tardive Dyskinesia

Clinical Findings

Dyskinesia is a general term simply meaning abnormal movements. Over the years, tardive dyskinesia has become synonymous with the first described complication of long-term dopamine receptor antagonist therapy: continuous, repetitive, rhythmical, stereotypic movements involving oral, buccal, and lingual areas. Prevalence estimates range from 0.5–65% in the literature, but is probably closer to 12% in patients on chronic haloperidol treatment. Older age, female gender, cumulative drug exposure, and the presence of an affective disorder are associated with increased prevalence of classical tardive dyskinesia; African-Americans appear to have a higher risk than Caucasians. In the past decade, the incidence of tardive dyskinesias may be in slight decline due to the use of second-generation D_2 antagonists, which demonstrate less receptor blocking affinity. On the other hand, children are increasingly treated for psychiatric symptoms using "atypical" neuroleptics, so the long-term incidence of tardive dyskinesia in this population must be carefully tracked.

Classical tardive dyskinesia causes a pattern of repetitive, complex chewing motions, occasionally with lip-smacking and opening of the mouth, tongue protrusion, lip pursing, and sucking movements. The mouth movements in classical tardive dyskinesia are readily suppressed by patients when they are asked to do so, and they cease during talking or eating. Because tardive dyskinesias do not interfere with basic functions, patients are often unaware of their movements. The constant lingual movements may lead to tongue hypertrophy, and macroglossia is a common clinical sign. Tardive dyskinesias may also cause limb movements, usually distal, repetitive, patterned choreic movements of the toes and fingers, the latter sometimes termed piano-playing movements. Sometimes, there is rhythmic rocking of the trunk.

Differential Diagnosis

The differential diagnosis of choreic movements of the face includes Huntington disease, idiopathic dystonia of the face (primary oromandibular dystonia, or Meige syndrome), senile and edentulous chorea of the face, branchial myoclonus, facial tics, and myokymia. In tardive dyskinesias, the pattern of the movements is typically rhythmic, repetitive, and stereotypical, in contrast to the orofacial chorea seen in Huntington disease, which is random and unpredictable.

Treatment

The most potent agents for treating tardive dyskinesias are catecholamine depletors and, paradoxically, DRBAs. The rationale for using dopamine-depleting drugs, such as reserpine and tetrabenazine, is that these agents effectively reduce dopaminergic synaptic activity, thereby reducing tardive dyskinesia symptoms, without exposing the brain to an offending DRBA. These agents are slowly titrated to the point of mild parkinsonism, usually reaching a dose range of reserpine 0.5–2 mg daily or tetrabenazine 25–100 mg daily. These agents may cause adverse effects that include parkinsonism, hypotension, akathisia, sedation, and depression, and are contraindicated in patients with depression.

The newer agent, valbenazine, a vesicular monoamine transporter type 2 [$VMAT_2$] treats tardive dyskinesia by reversibly impairing the dopamine transporter as it loads dopamine into synaptic vesicles for release, thereby reducing symptoms associated with dopamine hypersensitivity. Although tardive dyskinesia can be temporarily suppressed using increasing doses of DRBAs, continuing exposure to these agents may lead to worsening of the movements in the long term. α-Methylparatyrosine, a competitive inhibitor of tyrosine hydroxylase, is not very effective when used alone but can be a potent antidopaminergic drug when combined with other presynaptically acting drugs, such as dopamine depletors.

2. Tardive Dystonia

Clinical Findings

Tardive dystonia differs from tardive dyskinesias in that the movements are sustained and interfere with normal motor function. Just as DRBAs may induce acute dystonia, persistent, sustained, disabling dystonic movements may result from chronic DRBA exposure. Tardive dystonia, which resembles idiopathic dystonia, is more disabling than classical tardive dyskinesia. The combination of retrocollis, trunk arching backward, internal rotation of the arms, and extension of the elbows and flexion of the wrists is a frequently observed pattern in severely disabled patients. The onset of tardive dystonia

ranges from days to years after exposure to a DRBA. Severe tardive dystonia is more common in young men, whereas severe classical tardive dyskinesia is more common in older women.

Treatment

As with classical tardive dyskinesia, the most effective medications for tardive dystonia are antidopaminergic drugs, either dopamine depletors or DRBAs, but a smaller percentage of patients improves. As with classical tardive dyskinesia, increasing doses of DRBAs might temporarily help tardive dystonia, but continuing exposure may cause worse movements over time. In tardive dystonia, anticholinergics (eg, benztropine or trihexyphenidyl) are almost as effective as antidopaminergic drugs. The atypical antipsychotic, clozapine, is been helpful in some patients. For medically intractable tardive dystonia, bilateral globus pallidus interna [GPi] stimulation using implantable electrodes can be effective.

3. Tardive Akathisia

Clinical Findings

Tardive akathisia is a rare syndrome of restlessness and intolerance of remaining still, coupled with continuous, stereotyped, repetitive pacing and fidgeting movements. Tardive akathisia resembles acute akathisia in its subjective sense of intolerance or remaining still, and its outward manifestations of restlessness, except that the tardive form is persistent and may be permanent.

Treatment

Tardive akathisia can be helped by reserpine and tetrabenazine. In this respect, the clinical pharmacology more closely resembles that of classical tardive dyskinesia than acute akathisia. Opioids, such as codeine 15–60 mg daily, are reported to be beneficial in reducing the sensation of restlessness in chronic akathisia. Most of the patients develop tardive akathisia within the first 2 years of treatment.

Bhidayasiri R, Jitkrisadakul O, Friedman J, Fahn S. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. *J Neurol Sci* 2018; 1–9. [PMID: 29454493]

Factor SA, et al. Effects of valbenazine in participants with tardive dyskinesia: Results of the 1-year KINECT 3 extension study. *J Clin Psychiatry* 2017;78(9):1344–1350. [PMID: 29141124]

Hauser RA, et al. KINECT 3: A phase 3 randomized, double-blind placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry* 2017;174(5):476–484. [PMID: 28320223]

Savitt D, Jankovic J. Tardive syndromes. *J Neurol Sci* 2018;389: 35–42. [PMID: 29506749]

Stegmayer K, Walther S, van Harten P. Tardive dyskinesias associated with atypical antipsychotics: Prevalence, mechanisms and management strategies. *CNS Drugs* 2018;32(2):135–147. [PMID: 29427000]

NEUROLEPTIC MALIGNANT SYNDROME

ESSENTIALS OF DIAGNOSIS

- Fever, rigidity, and changes in mental status, with elevated muscle enzymes, dehydration, and autonomic instability
- The syndrome usually develops on stable therapeutic doses of DRBAs
- Must be distinguished from serotonin syndrome, malignant hyperthermia, acute generalized parkinsonism or dystonia ("dystonic storm"), and other causes of metabolic encephalopathy

Clinical Findings

Neuroleptic malignant syndrome (NMS) is an idiosyncratic, potentially life-threatening syndrome consisting of (1) hyperthermia, usually with other autonomic disturbances such as tachycardia, diaphoresis, and labile blood pressure; (2) extrapyramidal signs, usually muscle rigidity or dystonia, and often with elevated muscle enzymes; and (3) altered mental status, such as agitation, inattention, and confusion. The pathophysiologic mechanism of NMS and the individual susceptibility factors are not well understood.

NMS usually begins abruptly while the patient is on therapeutic, not toxic or supratherapeutic, dosages of antipsychotic medication. All the symptoms are fully manifest within 24 hours of onset and reach a maximum severity within 72 hours. There appears to be no relationship between the duration of therapy and the development of symptoms, as NMS can develop soon after the first dose or at any time after prolonged treatment. Recovery usually occurs within one to several weeks, but the syndrome is fatal in 20–30% of cases. Prolonged hyperthermia and generalized muscle contractions may cause rhabdomyolysis, with renal failure. Muscle biopsies show swelling, edema, and often vacuolar changes in muscle fibers. All agents that block dopamine D_2 receptors can induce NMS, including risperidone, olanzapine, aripiprazole, and other "atypical" neuroleptics; the only antipsychotics that do not induce NMS are clozapine, quetiapine, and pimavanserin. The differential diagnosis includes malignant hyperthermia, serotonin syndrome, and acute baclofen withdrawal, in addition to fever of any cause in the intensive care unit; the diagnosis depends on an accurate history of drug exposure and interactions.

Treatment

Treatment of NMS consists of discontinuing the DRBAs and providing supportive measures. Rapid relief of symptoms usually follows administration of dantrolene, bromocriptine, or levodopa. Reexposure to dopamine receptor antagonists does not necessarily lead to recurrence of NMS. Residual

catatonia lasting weeks to months has been reported after recovery from the acute syndrome, with some individuals responding to electroconvulsive therapy.

Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. *CNS Drugs* 2009;23:477–492. [PMID: 19480467]

RESTLESS LEGS SYNDROME

ESSENTIALS OF DIAGNOSIS

- A syndrome of restlessness and unpleasant sensations in the legs, which is relieved by moving or walking
- Associated with periodic limb movements of sleep
- Chronic, progressive course
- Responsive to dopamine agonists, opiates, and other agents

General Considerations

Thomas Willis, 17th century English physician, first described a condition of leg restlessness ("unquietness") and involuntary movements that interfered with sleep and was relieved by walking. As fully delineated by Ekbom, restless legs syndrome (RLS) is a chronic condition that usually begins during middle age and worsens with time. RLS is a circadian disorder that typically begins in the evening and may progressively worsen during the night. The disorder is common, affecting 3–10% of individuals. Many cases are familial, inherited in an autosomal dominant fashion. The cause of RLS is unknown, but the disorder is associated with iron-deficiency anemia, uremia, and peripheral neuropathy. RLS frequently responds to dopaminergic medication, implicating a role of central dopamine pathways in the pathophysiology of the disorder.

Clinical Findings

A. Symptoms and Signs

The key diagnostic features of RLS include ill-defined discomfort or unusual sensations ("dysesthesias") in the legs, sometimes described as intolerable tingling, crawling, creeping ["formication"], stretching, pulling, or prickling sensations (Table 15–20). Individuals with RLS usually do not describe their leg discomfort as painful muscular cramping or aching, a point of differentiation from nocturnal leg cramps. The legs are invariably involved, usually bilaterally, whereas the trunk and arms are rarely affected. RLS typically occurs during rest or sleep, or when patients are drowsy and attempting repose. The discomfort is associated with an irresistible urge to move the legs or walk about, which immediately relieves the unpleasant sensations. Symptoms typically begin intermittently and may be mild, but they may be debilitating and completely disruptive to sleep and necessitate medical intervention. Some patients experience leg restlessness during the day or in wakeful situations that involve immobility, such as sitting in an audience or air travel. Patients with PD may experience nocturnal parkinsonian akathisia after the last evening dose of levodopa wears off; this condition resembles RLS but lacks the signature leg paresthesias.

RLS has long been linked to periodic limb movements (PLMs), a movement disorder that occurs during sleep. The full cycle of these movements consists of brief jerks of either leg, dorsiflexion of the great toe and foot, and a briefly sustained tonic flexion spasm of the entire leg; the movement has the appearance of an exaggerated Babinski or flexor withdrawal reflex. The limb movements tend to recur every 20 seconds or so in trains that may last for hours. PLMs usually occur during stage 1 and stage 2 sleep and decrease in deeper sleep stages. Present in more than 80% of patients with RLS, PLMs also occur in other sleep disorders, including narcolepsy and REM behavior disorder, a condition of acting out vivid dreams.

In recent years, a number of genetic risk factors for RLS have been identified, although a specific causative gene has not yet been found. In families with RLS, the disorder is transmitted as an autosomal dominant trait. Several medical conditions are associated with an increased prevalence of RLS, including iron deficiency, uremia, peripheral neuropathy, diabetes, rheumatoid arthritis, pregnancy, gastric surgery, and the fibromyalgia syndrome. Patients with PD experience leg restlessness, but the true prevalence of RLS in PD is uncertain.

B. Laboratory Findings

Laboratory testing in RLS is aimed at identifying secondary causes of the syndrome. Iron studies and ferritin levels are the most important tests. Additional testing includes routine serum chemistry. Electrodiagnostic testing should be performed in patients with symptoms or signs of peripheral nerve dysfunction. In selected cases, a routine sleep study, or polysomnography, will reveal an increased amount of nocturnal movement and wakeful periods, delayed sleep onset, and PLMs of sleep.

Differential Diagnosis

It is important to distinguish RLS from akathisia, an intolerance of remaining still or sitting that may occur due to exposure to DRBAs or in PD. In RLS, the sensory discomfort and urge to move are localized to the legs, unlike in akathisia, which causes generalized discomfort or restlessness. RLS can be distinguished from nocturnal leg cramps, which cause painful muscle contractions, tightness, and tenderness. RLS must further be differentiated from peripheral neuropathy, radiculopathy, reflex sympathetic dystrophy, and other localized sensory disturbances that can involve the legs;

Table 15–20. Clinical features of restless legs syndrome.

Diagnostic Features
• Desire or need to move the limbs, usually associated with uncomfortable or unpleasant sensations
• Symptoms of motor restlessness
• Symptoms worse or exclusively present at rest, with at least partial or temporary relief by activity
• Symptoms maximal during evening and night
Typical Features
• Involuntary movements: periodic limb movements
• Sleep disturbance
• Normal neurologic examination
• Generally chronic course, often progressive
• Positive family history

in these disorders, the symptoms do not show the nocturnal predilection of RLS, and neurologic evaluation reveals nerve or root dysfunction. The painful legs and moving toes syndrome is an unusual and rare disorder that causes cutaneous pain and writhing, choreic toe movements, sometimes associated with peripheral neuropathy.

The differential diagnosis for PLMs comprises a wide variety of normal and abnormal movements in sleep, including hypnic jerks, normal postural shifts, nocturnal seizures, parasomnias such as sleep walking and pathologic arousals, and REM sleep behavior disorder.

Treatment

Several classes of medication are effective in RLS, including dopaminergic agents, opioids, benzodiazepines, and anticonvulsants, usually taken as a single dose before bed. The dopamine agonists pramipexole and ropinirole are first-line drugs for RLS. Unfortunately, dopamine drug treatment is sometimes associated with *rebound*, an increase in symptoms when the medication wears off; and *augmentation*, a progressively shorter latency to the onset of symptoms, necessitating earlier and higher dosing of dopaminergic medication. For this reason, calcium α-2-δ ligands (pregabalin, gabapentin), while less effective, are sometimes preferred over dopamine agonists for long-term therapy. Furthermore, dopamine agonists may trigger pathologic compulsive behaviors. For severe RLS, the opioids codeine, methadone, and naltrexone/naloxone can be effective, but these agents carry a risk of dependence. Clonazepam, carbamazepine, baclofen, and clonidine have all been reported as successful treatments for RLS. Because RLS symptoms are chronic and progressive, it is important to treat using the lowest effective doses. In patients with iron deficiency and RLS, treatment with iron is curative. Any treatment approach for RLS must also include optimization of sleeping habits.

Prognosis

The prognosis for RLS is generally good. Although the disorder is lifelong, small doses of medication and the development of optimal sleep hygiene usually keep the symptoms under control.

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