divided doses) is usually effective at relatively low doses, but higher doses may be effective in some patients. The drug is contraindicated in patients with bradycardia or asthma. Hand tremor tends to be most improved, while head tremor is often refractory. Primidone can be helpful but should be started at low doses (12.5 mg) and gradually increased (125–250 mg tid) to avoid sedation. Benefits have also been reported with gabapentin and topiramate. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with secondary muscle weakness. Surgical therapies targeting the VIM nucleus of the thalamus can be very effective for severe and drug-resistant cases.

DYSTONIA

CLINICAL FEATURES

Dystonia is a disorder characterized by sustained (>100 ms) or repetitive involuntary muscle contractions frequently associated with twisting and abnormal postures. Dystonia can range from minor contractions in an individual muscle group to severe and disabling involvement of multiple muscle groups. The frequency is estimated to be 300,000 cases in the United States but is likely to be much higher because many cases are not recognized. Dystonia is often brought out by voluntary movements (action dystonia) and can extend to involve muscle groups and body regions not required for a given action (overflow). It can be aggravated by stress and fatigue and attenuated by relaxation and sensory tricks such as touching the affected body part (geste antagoniste). Dystonia can be classified according to age of onset (childhood vs adult), distribution (focal, multifocal, segmental, or generalized), or etiology (primary or secondary).

PRIMARY DYSTONIAS

At least 16 gene mutations are associated with dystonia and classified as *DYT1–DYT16*. Idiopathic torsion dystonia (DYT1) or Oppenheim's dystonia is predominantly a childhood-onset form of dystonia with an autosomal dominant pattern of inheritance that primarily affects Ashkenazi Jewish families. The majority of patients have an age of onset younger than 26 years (mean 14 years). In young-onset patients, dystonia typically begins in the foot or the arm and in 60–70% progresses to involve other limbs as well as the head and neck. In severe cases, patients can suffer disabling postural deformities that compromise mobility. Severity can vary within family members, with some affected relatives having severe disability and others a mild dystonia that may not even be appreciated. Most childhood-onset cases are linked to a mutation in the *DYT1* gene located on chromosome 9q34, resulting in a trinucleotide GAG deletion with loss of one of a pair of glutamic acid residues in the protein torsin A. *DYT1* mutations are found in 90% of Ashkenazi Jewish patients with DYT1 dystonia and probably relate to a founder effect that occurred about 350 years ago. There is variable penetrance, with only about 30% of gene carriers expressing a clinical phenotype. Why some gene carriers express dystonia and others do not is not known. The function of torsin A is unknown, but it is a member of the AAA^+ (ATPase) family that resembles heat-shock proteins and may be related to protein processing and transport. The precise pathology responsible for DYT1 dystonia is not known.

Dopa-responsive dystonia (DRD) or the Segawa variant (DYT5) is a dominantly inherited form of childhood-onset dystonia caused by a mutation in the gene that encodes GTP cyclohydrolase-I, the rate-limiting enzyme for the synthesis of tetrahydrobiopterin. This mutation leads to a defect in the biochemical synthesis of tyrosine hydroxylase, the rate-limiting enzyme in the formation of dopamine. DRD typically presents in early childhood (1–12 years) and is characterized by foot dystonia that interferes with walking. Patients often experience diurnal fluctuations, with worsening of gait as the day progresses and improvement with sleep. DRD is typified by an excellent and sustained response to small doses of levodopa. Some patients may present with parkinsonian features, but can be differentiated from juvenile PD by normal striatal dopamine imaging and the absence of levodopa-induced dyskinesias. DRD may occasionally be confused with cerebral palsy because patients appear to have spasticity, increased reflexes, and Babinski responses (which likely reflect a dystonic contraction rather than an upper motor neuron lesion). Any patient suspected of having a childhood-onset dystonia should receive a trial of levodopa to exclude this treatable condition.

Mutations in the *THAP1* gene (DYT6) on chromosome 8p21q22 have been identified in Amish families and are the cause of as many as 25% of cases of non-DYT1 young-onset primary torsion dystonia. These patients are more likely to have dystonia beginning in the brachial and cervical muscles, which later can become generalized and associated with speech impairment. Myoclonic dystonia (DYT11) results from a mutation in the epsilon-sarcoglycan gene on chromosome 7q21. It typically manifests as a combination of dystonia and myoclonic jerks, frequently accompanied by psychiatric disturbances.

FOCAL DYSTONIAS

These are the most common forms of dystonia. They typically present in the fourth to sixth decades and affect women more than men. The major types are as follows: (1) *blepharospasm*—dystonic contractions of the eyelids with increased blinking that can interfere with reading, watching television, and driving. This can sometimes be so severe as to cause functional blindness. (2) *Oromandibular dystonia* (OMD)—contractions of muscles of the lower face, lips, tongue, and jaw (opening or closing). Meige's syndrome is a combination of OMD and blepharospasm that predominantly affects women older than age 60 years. (3) *Spasmodic dysphonia*—dystonic contractions of the vocal cords during phonation, causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly, the abductors are affected, leading to speech with a breathy or whispering quality. (4) *Cervical dystonia*—dystonic contractions of neck muscles causing the head to deviate to one side (*torticollis*), in a forward direction (*anterocollis*), or in a backward direction (*retrocollis*). Muscle contractions can be painful and associated with a secondary cervical radiculopathy. (5) *Limb dystonias*—these can be present in either arms or legs and are often brought out by task-specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp), or putting (the yips). Focal dystonias can extend to involve other body regions (about 30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic in origin. Their cause is not known, but genetic factors, autoimmunity, and trauma have been suggested. Focal dystonias are often associated with a high-frequency tremor that resembles ET. Dystonic tremor can usually be distinguished from ET because it tends to occur in conjunction with the dystonic contraction and disappears when the dystonia is relieved.

SECONDARY DYSTONIAS

These develop as a consequence of drugs or other neurologic disorders. Drug-induced dystonia is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients and may be acute or chronic (see below). Secondary dystonia can also be observed following discrete lesions in the striatum and occasionally in the pallidum, thalamus, cortex, and brainstem due to infarction, anoxia, metabolic disorders, trauma, tumor, infection, or toxins such as manganese or carbon monoxide. In these cases, dystonia often assumes a segmental distribution, but it can be generalized when lesions are bilateral or widespread. More rarely, dystonia can develop following peripheral nerve injury and be associated with features of complex regional pain syndrome (Chap. 454). A psychogenic origin is responsible for some cases of dystonia presenting with fixed, immobile dystonic postures (see below).

DYSTONIA PLUS SYNDROMES

Dystonia may occur as a part of another neurodegenerative conditions such as Huntington's disease, PD, Wilson's disease, corticobasilar ganglionic degeneration, PSP, the Lubag form of dystonia-parkinsonism (DYT3), and mitochondrial encephalopathies. In contrast to the primary dystonias, dystonia is usually not the dominant neurologic feature in these conditions.

PATHOPHYSIOLOGY OF DYSTONIA

The pathophysiologic basis of dystonia is not completely known. The phenomenon is characterized by co-contracting synchronous bursts of agonist and antagonist muscle groups with recruitment of