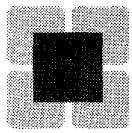

Benzodiazepines in the treatment of movement disorders

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HYPERKINETIC movement disorders are characterized by involuntary, abnormal, or excessive movements. Each type of movement may be associated with several different diseases, and combinations of movement types are common (eg, tremor and myoclonus may occur with dystonia). Moreover, dysfunction in a variety of sites in the nervous system may result in the same symptom (eg, myoclonus, chorea, or tremor). Because of these complex interactions, understanding the physiological and pharmacological basis of movement disorders is difficult. Despite incomplete knowledge, many hyperkinetic symptoms can be effectively treated.

Benzodiazepines play a role in the treatment of many movement disorders. In tics and myoclonus, they play a major role. Although in dystonic syndromes benzodiazepines benefit a minority of patients, they may contribute significantly to the quality of life. In conditions such as essential tremor (ET), chorea, tardive dyskinesias and other disorders, the role of benzodiazepines is controversial. The treatment strategies for several movement disorders in which benzodiazepines play an important role are outlined below.

TICS

Tics are involuntary, spontaneous, purposeless, often complex movements or vocalizations that abruptly interrupt normal motor activity. The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR)* has described several categories of tic disorders: Tourette's syndrome, chronic motor or vocal tics, transient tic disorder, and tic disorder not otherwise specified. The clinical usefulness of these categories is controversial. Although the presence of vocal as well as motor tics—the hallmark of Tourette's syndrome—may be socially disabling, it may not have other implications for prognosis and treatment. Patients with otherwise typical motor and vocal tics may have onset of the condition over by age 21 (the maximum age for onset of Tourette's syndrome). Most studies have found chronic motor and vocal tics and transient tics to be genetically related to Tourette's syndrome.[1] Recent evidence suggests that the majority of tic cases are inherited and that there is autosomal dominant transmission with sex-specific variable penetrance.[2]

Features which are frequently associated with tics can aid in the recognition of a tic disorder. Most patients have an unpleasant physical sensation or sense of discomfort preceding the tic, and the discomfort is temporarily relieved by the tic. Individual tics often wax and wane in intensity over weeks to months. Many patients can temporarily suppress their tics; however, in those with severe tics, the tics may be present constantly and be unsuppressible. After suppression of tics, many patients will experience a rebound flurry of tics. Onset in childhood or adolescence and a family history of tics or of obsessive/compulsive behaviors are common, but exceptions do occur. Other associated features include attention deficit, hyperactivity, learning disorders, obsessive-compulsive symptoms, sleep problems, palilalia, and echolalia.

The phenomenology of tics has recently been reviewed.[3] Common motor tics include eye blinking,

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eye deviations, eyebrow raising, grimacing, head tossing, shoulder shrugging, abdominal or buttock tensing, jumping, skipping, obscene gestures, and combinations of these movements. Common phonic or vocal tics include grunting, coughing, sniffing, throat clearing, tongue clicking, nonsense phrases, speech fragments, and coprolalia.

Treatment

Many medications have been tried in an attempt to control tics, but only three—clonidine, clonazepam, and the antidopaminergic agents—have been found to be clinically effective. Since these medications provide only symptomatic relief, patients with mild or tolerable tics need not be treated. However, even when tics are mild, associated behavioral problems may be disabling and require treatment. These include attention deficit, hyperactivity, obsessive-compulsive symptoms, and depression. Treatment of these associated problems, education about the nature of tics, and support at school for individuals with learning problems may be more helpful than treating the tics themselves.

If tics require treatment, *clonidine* is generally recommended as the first line of therapy, particularly for children with behavioral problems and vocal tics. Although its efficacy has been challenged in a recent double-blind study,[4] clonidine is usually well tolerated and does not produce persistent side effects. Most studies have found that approximately 40% to 50% of patients with tics respond to clonidine.[5,6] It has also been suggested that clonidine may help behavioral problems even when tics do not improve, and that children, especially those with phonic tics, may be most responsive to clonidine.[7]

Clonidine should be initiated at a low dose of 0.05 mg/day and slowly increased to doses in the range of 0.1 to 0.8 mg/day. Therapeutic benefit may not be seen for 2 to 3 months or longer. If the drug needs to be discontinued, it should be tapered slowly because of the risk of rebound hypertension. Clonidine may produce sedation and dry mouth. Although postural hypotension is usually not a problem, blood pressure does need to be monitored.

Clonazepam is the second choice when treatment of tics is indicated. It can be added to clonidine or substituted for it. There are several studies documenting the efficacy of clonazepam.[6,8,9] Two of these trials found clonazepam to be somewhat more effective than clonidine, with as many as 30% of patients having marked improvement.[6,9] It was also suggested that clonazepam had been particularly effective for motor tics and in adults.[6,9]

Clonazepam is usually initiated at a dose of 0.25 mg/day and increased weekly by 0.25 to 0.5 mg/day to a maintenance dose of about 4.0 to 5.0 mg daily. Side effects include drowsiness, decreased concentration, and personality change (the "nasty syndrome"); they may be seen acutely or after chronic treatment and are reversible if the medicine is discontinued or the dose lowered.

In cases in which clonidine and clonazepam are insufficient, *antidopaminergic* agents should be tried. Dopamine depletors such as alphamethylparatyrosine (metyrosine), reserpine, and tetrabenazine do not induce persistent dyskinesias and are therefore preferred over dopamine receptor blockers or neuroleptics. However, only tetrabenazine, which is investigational in the United States, has been reported to be effective.[6] Side effects such as depression, drowsiness, and reversible, drug-induced parkinsonism are common with all antidopaminergics.

Haloperidol has been used for control of tics since 1961 and has been found to be effective in 60% to 80% of patients. Reversible side effects include irritability, depression, loss of motivation, mental dullness, akathisia, parkinsonism, school phobia, weight gain, and xerostomia. In one survey, 50 of 60 (83%) patients reported side effects and 20 of 60 (33%) patients had to discontinue the drug.[10] Other neuroleptics such as pimozide[11] and fluphenazine[10] are comparable to haloperidol in efficacy and may have fewer reversible side effects. These agents have the potential for producing severe, long lasting, or permanent involuntary movements (tardive dyskinesias) and should therefore be used only in severe cases when all other agents fail.[12]

Neuroleptic therapy should begin with low doses and be gradually increased to typical maintenance doses of 4 to 10 mg daily in 2 to 3 divided doses. Because of the risk of tardive dyskinesias, these agents must be used in the minimum possible dose. The required dose may vary as the underlying tics wax and wane, and attempts should be made periodically to reduce or eliminate the medication. The addition of clonidine or of clonazepam to neuroleptics may provide better control than the use of a single neuroleptic agent in high doses. Since tics often decrease in severity during late adolescence, chronic use of neuroleptic agents may not be required. When symptoms are tolerated, the agent may be discontinued. It is strongly recommended, however, that whenever possible neuroleptics be tapered off slowly.

TABLE 1
CLASSIFICATION OF DYSTONIC SYNDROMES

I. Primary dystonia
   1. Levodopa-responsive dystonia (diurnal dystonia, Segawa variant)
   2. Focal dystonia (torticollis, blepharospasm, oromandibular dystonia, occupational cramps, spastic dysphonia)
   3. Segmental, multifocal and generalized dystonia
   4. Hemidystonia
   5. Paroxysmal dystonias (kinesigenic, nonkinesigenic and nocturnal paroxysmal dystonia)
II. Secondary dystonia
   1. Wilson's disease
   2. Intracerebral lesion (tumor, arteriovenous malformation, etc.)
   3. Tardive dystonia (after exposure to dopamine receptor blocking agents)
   4. Acute dystonic reactions (after exposure to dopamine receptor blocking agents)
   5. Other drug exposure (anticonvulsants, calcium channel blockers, levodopa, dopamine agonists, etc.)
   6. Psychogenic dystonia
   7. Many other conditions

DYSTONIA

Dystonia is characterized by sustained involuntary muscle contractions that are usually of a twisting and repetitive nature. Dystonia posturing is often action-induced when the disease is mild, and the posturing may be present only with specific actions. When severe, dystonia may persist at rest.

Dystonic syndromes can be classified by etiology (primary or idiopathic vs secondary or symptomatic), by inheritance pattern (sporadic, autosomal dominant, or x-linked recessive), by age at onset (childhood, juvenile, or adult), and by sites of involvement (focal, segmental, generalized, or hemidystonia or involvement of ipsilateral arm and leg). *Table 1* provides a brief classification of dystonic conditions, oriented towards specific treatment strategies.

Treatment of primary (idiopathic) dystonia

1. *Diurnal dystonia* (levodopa-responsive dystonia) is generally familial, usually starting in childhood with gait disturbance.[13] Patients may have signs of parkinsonism (bradykinesia and loss of postural reflexes), corticospinal tract signs (including Babinski signs), and diurnal variation (dramatic improvement after sleep). These patients often improve dramatically on 200 to 300 mg of levodopa, daily, in the form of carbidopa/levodopa. Since some individuals lack one or more of the typical features of this condition, all patients with idiopathic dystonia starting in childhood or young adulthood should be treated initially with levodopa, in the form of carbidopa/levodopa, for at least two weeks. Many patients require very small doses of levodopa and some will develop repetitive movements (levodopa dyskinesias) on higher doses. Although these dyskinesias are reversible and disappear on smaller doses, it is still best to start with 100 mg/day of levodopa, in divided doses, and increase the dose gradually.

2. Many *focal dystonias* improve with injections of botulinum toxin type A (Botox). The efficacy of Botox has been documented by double-blind, placebo-controlled studies for the treatment of blepharospasm[14,15] and torticollis[15–18] and in open studies for ormandibular dystonia,[19] spastic dystonia,[20] and writer's cramp.[21] Botox interferes with the release of acetylcholine from cholinergic nerve terminals and creates muscle weakness lasting from 3 to 6 months. When Botox is injected intramuscularly or subcutaneously over a muscle, dystonic contractions may be dramatically reduced without severely compromising normal functioning. No clinically significant effects have been observed in muscles distant from the site of injection in a decade of use. The local side effects of Botox injections are transient (see below). Even though disability in some children may result from dystonia in a single site, chronic Botox injections are not recommended for pediatric patients. Until the safety of chronic injections is established, pharmacotherapy is preferred for treating children.

Spastic dysphonia (laryngeal dystonia) improves dramatically in over 90% of cases with tiny doses of Botox (2.5 to 3.75 units of toxin activity) injected into both vocalis muscles through a hollow core electromyographic (EMG) needle, with EMG verification of needle tip placement. Blepharospasm (upper facial dystonia) improves in 80% to 90% of cases after the subcutaneous injection of approximately 25 units of Botox around each eye, and EMG guidance is not required. Torticollis (dystonic head movement) requires much higher doses of the toxin (up to 450 units) injected into the sternocleidomastoid, splenius capitus, trapezius, and other contracting muscles to achieve reasonable benefit. Approximately 60% to 75% of patients will experience significant benefit lasting about 3 months.[17]

The benefit from Botox injections lasts 3 to 6 months, at which time patients can be reinjected. Only local side effects have been seen with these injections: transient breathiness or swallowing difficulty after vocal cord injections, transient ptosis after eyelid injections, and excess neck weakness after neck injections. After injections in high doses to the neck, some patients will experience malaise, generalized aching, nausea and

headache, although actual weakness of uninjected muscles has not been seen. Since some patients with torticollis have developed sufficient titers of antibotulinum toxin antibodies to block the effects of Botox, it is best to use the smallest doses possible and inject as infrequently as feasible.

Writer's cramp (brachial dystonia), oromandibular and lower facial dystonias may also improve after EMG guided Botox injections in selected patients; however, selecting muscles and doses does require special experience. Injections into the tongue for lingual dystonia may be beneficial, but since the procedure has been associated with dysphagia and aspiration, it should not be done routinely.

Patients with focal dystonia who fail to improve with Botox injections can be treated with pharmacotherapy.

3. *Segmental, multifocal, and generalized dystonia* can be treated with pharmacotherapy. Anticholinergic agents are the most likely to be effective.[22] The efficacy of high-dose anticholinergics has been documented by double-blind trial.[23] In children, 2.5 mg of trihexyphenidyl is started once daily and increased weekly by 2.5 mg/day, q.i.d., to tolerance. In adults, ethopropazine produces fewer side effects and can be increased on a similar schedule, substituting 25 mg of ethopropazine for 2.5 mg of trihexyphenidyl. Since the benefit from anticholinergic agents may be delayed in onset, after each month or so of increasing doses patients should be observed for several weeks on a constant dosage. Benefit may be seen at a total daily dosage of 20 mg or more of trihexyphenidyl (200 mg of ethopropazine). Children tolerate high doses of anticholinergic medicine (often greater than 80 mg/day of trihexyphenidyl) and about 2 in 3 will improve their symptoms. Adults, on the other hand, tolerate these agents poorly and only about 2 in 5 will improve to some degree.[22,23]

Peripheral anticholinergic side effects such as dry mouth, blurred vision, constipation, and urinary retention may be treated with oral pyridostigmine and/or pilocarpine eye drops. A few patients complain of short-lived benefit after each dose of anticholinergic medicine or of developing side effects shortly after taking their dose. A time-release preparation of trihexyphenidyl is available and has been helpful in these cases. Memory loss or confusion requires a trial of the time-release preparation or dose reduction.

Although anticholinergic agents are the most likely to be effective in segmental, multifocal and generalized dystonia, other agents may produce substantial benefit in some cases. Patients may also get additive benefit from multiple agents. We conducted a retrospective review of patients treated at the Movement Disorder Center of Columbia-Presbyterian Medical Center in New York.[22] Most patients were treated first with anticholinergics; if this therapy was inadequate, other agents were added or substituted. Baclofen and clonazepam produced benefit in about 10% to 20% of patients (*Table 2*). Baclofen seemed to be particularly effective in adults with cranial dystonia and in some children.[24] Patients may have fewer side effects with other benzodiazepines, and these can be tried if clonazepam produces benefit but is not tolerated. Even though carbamazepine benefits a very small percentage of patients with dystonia, it can produce dramatic improvement on occasion.

TABLE 2
TREATMENT OUTCOME IN IDIOPATHIC DYSTONIA: PERCENTAGE OF PATIENTS WHO IMPROVED

Drug	Type of dystonia		
	All	Segmental	Generalized
Anticholinergic	43% (N=227)	35% (N=71)	50% (N=46)
Baclofen	20% (N=108)	24% (N=33)	14% (N=8)
Clonazepam	16% (N=115)	17% (N=35)	6% (N=17)
Carbamazepine	11% (N=62)	not studied	not studied
Other benzodiazepines	13% (N=40)	not studied	not studied

Dopamine depletors and dopamine receptor blocking agents are also useful in the treatment of dystonia. They can cause drowsiness, orthostatic hypotension, depression, and parkinsonism but may also benefit some patients with idiopathic dystonia.[25] The combination of a dopamine depletor, a dopamine receptor blocker, and an anticholinergic agent may be useful when other agents fail.[26] Because of the risk of developing tardive complications with chronic administration, the use of dopamine receptor blocking agents should be avoided if possible. These agents should be reserved for severe, disabling dystonia after all other medications have failed.

Tetrabenazine is an investigational dopamine-depleting agent with a small amount of dopamine receptor blocking activity. It has never been associated with the development of tardive complications. Alone or in combination with lithium, it benefits some patients with dystonia.[27] In addition to the complications associated with dopamine depletors, some pa-

tients develop acute akathisia (restlessness) from tetrabenazine. The akathisia always resolves if tetrabenazine is discontinued and may improve with propranolol.[28]

Levodopa and dopamine agonists such as bromocriptine worsen dystonia in some patients who do not have diurnal dystonia (levodopa-responsive dystonia). Paradoxically, these medications may also reduce symptoms.[29] Patients without diurnal dystonia who improve with dopaminergic drugs require large doses to achieve significant benefit.

4. *Hemidystonia* is most commonly found in secondary dystonia, but occasionally patients with idiopathic dystonia will have persistent hemidystonia or predominantly unilateral symptoms. If all measures described above fail, these individuals may benefit from thalamotomy.[30] Patients with bilateral or axial dystonia who fail medical therapy may also benefit from bilateral thalamotomies but, in addition to a small risk of infarct or hemorrhage, bilateral thalamotomies involve a substantial risk of speech impairment. Thalamotomy should therefore only be considered in the most disabled patients, after extensive conservative measures have failed.

Many operations lesioning the peripheral nervous system have been used to relieve the symptoms of a variety of focal dystonias. Although most have been superseded by medical therapies, they may still benefit a patient with extremely severe focal dystonia who has failed on all non-surgical therapies.

5. *Paroxysmal dystonias* can be divided into kinesigenic (brief, multiple attacks usually triggered by sudden movements), nonkinesigenic (more prolonged attacks unrelated to movement), and nocturnal paroxysmal dystonia (attacks of dystonia during sleep of variable duration, which may or may not be accompanied by dystonia while awake). The kinesigenic variety usually improves dramatically with anticonvulsant agents such as carbamazine or phenytoin.[31] The nonkinesigenic type is difficult to treat. Anticonvulsants and acetazolamide[32] should be tried. One patient, reported to respond only transiently to high-dose diazepam, subsequently had sustained benefit from therapy with the short-acting benzodiazepine oxazepam, on alternate days.[33] If these treatments fail, the agents used for nonparoxysmal dystonia can be tried. Nocturnal paroxysmal dystonia may respond to carbamazepine, especially when the attacks are brief.[34] It should be also noted that some patients with nonkinesigenic paroxysmal dystonia have a psychogenic etiology[35] and require psychotherapy.

Treatment of secondary (symptomatic) dystonia

When possible, the conditions underlying secondary dystonia should be treated. If necessary, the symptomatic treatment for secondary dystonia can proceed as outlined for primary (idiopathic) dystonia; but the response is, in general, inferior. There are, however, some exceptions:

1. *Secondary focal dystonia* from a variety of causes has been found to improve with Botox injections.

2. *Tardive dystonia*—persistent dystonia induced by dopamine receptor blocking agents or dystonia in neuroleptic-dependent psychiatric patients—can be treated with anticholinergic or dopamine-depleting agents. Approximately 50% of patients with tardive dystonia will improve when treated with high-dose anticholinergic agents, dopamine depletors (reserpine, metyrosine, or tetrabenazine) or a combination of an anticholinergic and a dopamine depletor.[36] Underlying depression is not an absolute contraindication to the use of dopamine depletors, since patients may become less depressed when their dystonic symptoms improve. Some patients, however, develop drug-induced parkinsonism as the dystonic symptoms improve. If the parkinsonism is mild, it may be better tolerated than the tardive dystonia.

3. *Acute dystonic reactions* produced by dopamine receptor blocking agents usually do not persist for long after the agent is stopped. When severe, they can be treated with either anticholinergics, antihistamines, or benzodiazepines. These drugs can be given intramuscularly or intravenously for rapid control of severe symptoms.

MYOCLONUS

Myoclonus refers to a brief, shock-like muscle jerk. This jerk is usually produced by a brief muscle contraction; but a brief lapse of muscle contraction may also cause a shock-like jerk (asterixis)—which is considered a "negative" myoclonus. Like dystonia, myoclonus is classified by etiology (primary vs secondary), by inheritance pattern (sporadic vs inherited), and by the body region affected (focal, multifocal, segmental, and generalized). Myoclonus may also be (1) rhythmic or arrhythmic; (2) spontaneous or induced (by action or other triggers); and (3) synchronous or asynchronous (when more than one body region is involved). Dysfunction in the cerebral cortex, subthalamus, cerebellum, brainstem, spinal cord, and even in the peripheral nervous system[37] may cause myoclonus. Although the

muscle jerk may be the only symptom in a myoclonic syndrome, it may also be accompanied by seizures, static or progressive encephalopathy, cerebellar deficits, as well as other neurologic signs and symptoms.

Since primary myoclonus is uncommon, thorough evaluation for an identifiable etiology should always be undertaken. There are many causes of myoclonus, including degenerative diseases, metabolic and toxic conditions, focal damage to the nervous system (from vascular disease, tumors, trauma, etc.), and hypoxia.[38] Full understanding of the biochemical and physiological basis of myoclonus has yet to be established. Nevertheless, effective symptomatic treatment is often possible. Only the treatment of nonepileptic myoclonus is discussed below.

Treatment

Clonazepam is the single most effective treatment for myoclonus. It is unclear whether its therapeutic benefit is due to enhanced GABA-mediated (gamma-aminobutyric acid) inhibition or to serotonergic effects. For unknown reasons, clonazepam is significantly more potent as an antimyoclonic agent than benzodiazepines such as diazepam or chlordiazepoxide.[39] Clonazepam has been employed in various subtypes of myoclonus including cortical, subcortical, palatal, and spinal myoclonus.[40,41] The usual starting dosage is 0.25 to 0.5 mg at bed time; the dosage is increased weekly by 0.5 mg/day. The usual therapeutic dosage is 3 to 6 mg/day t.i.d., but doses up to 20 mg/day have been successfully used. Side effects include drowsiness, lethargy, ataxia, and—at high doses—personality change with irritability or aggressive behavior.

If therapy with clonazepam is insufficient, sodium valproate should be added. The initial dosage is 250 mg/day; the daily dosage is increased by 250 mg every 4 to 7 days, up to a maximum of 60 mg/kg/day. In general, the therapeutic dosage of valproate for myoclonus ranges between 1,200 and 1,500 mg/day. Gastrointestinal (GI) side effects may occur; the GI symptoms may be ameliorated by taking the drug with meals or switching to an enteric-coated preparation. Hepatotoxicity needs to be carefully monitored.

If clonazepam and valproate are not sufficiently effective or not tolerated, 5-hydroxytryptophan (5-HTP) and carbidopa may be effective. Carbidopa needs to be given with 5-HTP in order to block nausea, vomiting and diarrhea due to peripheral conversion of 5-HTP to serotonin. For the first several days of treatment, carbidopa (50 mg q.i.d. is given alone. Then, 5-HTP is added at 25 mg/day and increased by 25 to 50 mg/day q.i.d. dosing every 3 to 4 days. A maximum of 3 grams/day has been given, but dramatic benefit may occur with half this dosage. Specific antiemetic and antidiarrheal treatment may be required (avoiding neuroleptics). Central side effects of hypomania, restlessness, and agitation may also be seen. The serotonin re-uptake blocker fluoxetine may enhance the action of 5-HTP.[42]

Occasional patients with myoclonus may respond to other agents. Anticholinergics[43,44] and tetrabenazine[40] have been reported to produce improvement in some patients with myoclonus. The dopamine (and serotonin) agonist lisuride was reported to be of benefit in cortical myoclonus.[45]

TREMOR

Essential tremor (ET)

Tremor is the rhythmic oscillation of a body part. Essential tremor (ET) is a postural tremor in a patient who lacks the features of Parkinson's disease, cerebellar disease, or other known cause of tremor. The ET is most commonly present in the upper extremities, although the head and voice are sometimes involved and, rarely, the trunk and lower extremities; even the tongue or chin may be involved.[46] The tremor is usually slowly progressive, sometimes familial, and it often improves dramatically, but transiently, after alcohol ingestion.

Beta adrenergic antagonists are considered the drugs of choice for the treatment of ET. Propranolol (up to 240 mg/day) produces a reduction in tremor amplitude in many patients with ET, and functional improvement in others. These effects have been documented in double-blind, placebo-controlled studies.[47–50] Unfortunately, few individuals receive dramatic benefit from beta blockers, and many patients also tend to lose benefit with time. Beta blockers are often well tolerated in high doses. The more common side effects are impotence in men, depression, fatigue, and weight gain. Congestive heart failure, bronchial asthma and diabetes mellitus are contraindications to the use of beta blockers.[51]

The anticonvulsant agent primidone has also been shown—in double-blind, placebo-controlled studies—to benefit many patients with ET.[52] Although the magnitude of improvement with primidone may be more dramatic than that seen with beta blockers, patients may lose its benefit with time. Some individuals have dramatic improvement with low doses of

primidone (as little as 50 mg/day), but higher doses may be required for others. In some patients the optimal dosage has been found to be 1,000 mg/day.[53] Many patients will not tolerate high doses of primidone due to sedation, confusion, and ataxia. A minority of patients will have a severe, toxic reaction consisting of ataxia, dysphoria, drowsiness, and nausea after a single dose of as little as 50 mg. This reaction can be avoided by starting with 25 mg or even 12.5 mg of primidone and gradually increasing the dose.

Despite the proven effectiveness of beta blockers and primidone, many patients with ET will fail to get sustained, functionally significant improvement from either agent; some patients may benefit from a combination of primidone and a beta blocker. Even though a controlled study found clonazepam to be ineffective in an unselected population,[54] an uncontrolled study found clonazepam to be helpful in patients with a prominent intention component to their tremor.[55]

Thalamotomy may benefit patients with ET.[56] However, in addition to the small risk of stroke or cerebral hemorrhage, bilateral thalamotomy carries a more substantial risk of speech impairment. Thalamotomy should be reserved for patients with severe tremor who fail medical therapy and, except in extraordinary cases, for those who would benefit from unilateral improvement in tremor.

Orthostatic tremor

Orthostatic tremor was first recognized as a disease entity (and named) by Heilman in 1984.[57] Patients with this peculiar gait disorder experience crescendo tremor of the legs while standing and relief by walking. A high frequency tremor of the legs (14 to 18 Hertz) can be recorded in many individuals with this condition.[58] Despite the small number of case reports, this diagnosis has been made with increasing frequency since the condition was defined, and its true prevalence may be underestimated. Typical ET and typical orthostatic tremor may appear in members of the same family,[59,60] and some patients may experience orthostatic tremor with ET of the upper extremities. These findings have prompted the suggestion that orthostatic tremor is a variant of ET.[59,60] Few treatment results have been reported in this condition; successful therapy has been reported most often with clonazepam,[57,59,60] even though some patients have not sustained its initial benefit.[60,61]

CHOREA

Chorea refers to a flowing pattern of irregular muscle jerking. It occurs in a variety of disorders including degenerative diseases (Huntington's disease and neuroacanthocytosis), vascular disease (hemichorea or hemiballismus), parainfectious conditions (Sydenham's chorea) and inflammatory states (systemic lupus erythematosus chorea).

Specific and effective control of chorea can often be achieved with antidopaminergic medications.[62,63] These agents may be poorly tolerated due to depression, akathisia, or drug-induced parkinsonism; agents with dopamine-receptor blocking activity may induce permanent tardive movements. Although the efficacy of benzodiazepines for treating chorea is not generally accepted, they have been used for this purpose.[64,65] Benzodiazepines may have a role, however, in the treatment of self-limited chorea such as Sydenham's chorea or when other agents are not tolerated.

DRUG-INDUCED DYSKINESIAS

Drug-induced dyskinesias may occur after exposure to a large number of drugs; they most commonly occur after exposure to neuroleptic agents (tardive dyskinesias) or during treatment of Parkinson's disease. Tardive dyskinesias often improve with dopamine depleting agents,[66] but, as already noted, these medications may not be tolerated due to side effects. One study found benzodiazepines to be an effective therapy for tardive movements,[67] but those results remain to be confirmed.

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