

Treatment of hyperkinetic movement disorders

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Parkinson's disease, the most common hypokinetic movement disorder, has received much attention from the clinical and scientific community, but there has been a relative paucity of comprehensive reviews of hyperkinetic disorders, even though they are equally or even more disabling. Hyperkinetic movement disorders include tremors, dystonia, chorea, tics, myoclonus, stereotypies, restless legs syndrome, and various other disorders with abnormal involuntary movements. Substantial progress has been made in the understanding of the role of the basal ganglia in the pathophysiology of these hyperkinesia disorders and in motor control, muscle tone, posture, and cognitive processes. Although therapies that target pathogenesis are still lacking, effective management of hyperkinetic movement disorders demands that physicians are knowledgeable about current and novel pharmacological and surgical approaches. In addition to tetrabenazine, a monoamine-depleting drug, new formulations of botulinum toxin are being increasingly used in the treatment of these movement disorders. Finally, success with surgical approaches, particularly deep brain stimulation in patients with Parkinson's disease who have levodopa-induced dyskinesias, has been extended to the treatment of many hyperkinetic movement disorders.

Introduction

Movement disorders are categorised as a group of neurological symptoms, signs, or diseases that manifest as either slowness and paucity of movement (hypokinesias; typically seen in Parkinson's disease and other parkinsonian disorders) or by excessive, abnormal involuntary movements (hyperkinesias). Hyperkinetic movement disorders include tremors, dystonia, chorea, ballism, athetosis, tics, myoclonus and startle syndromes, hemifacial spasm, stereotypies, akathisia, and various other movement disorders.¹ The crucial role of the basal ganglia, not only in hyperkinetic movement disorders, but also in motor control, muscle tone, posture, behaviour, and cognition, is being increasingly recognised.

In this Review, the treatment of the most common hyperkinetic movement disorders encountered in a movement disorders clinic (table) is discussed, particularly tremors, dystonia, tics, and chorea. Readers are referred to the panel and other sources^{1,49–50} for references on treatments of other hyperkinesias, such as levodopa-induced dyskinesias in patients with Parkinson's disease, restless legs syndrome,^{40–45} myoclonus,^{46,47} painful legs and moving toes syndrome,⁴⁸ hemifacial spasm, and other peripherally induced movement disorders.⁵¹ Similarly, psychogenic hyperkinetic movement disorders, an increasingly important area of crossover between neurology and psychiatry, are not discussed, but readers are referred to recent publications on this topic.^{52,53} Here, therapeutic strategies guided not only by evidence-based data but also by long-term, observational, and personal experience are highlighted because findings from well designed, randomised clinical trials are often lacking. New medications, use of various botulinum toxin products, and surgical treatments are also critically reviewed. A practical approach tailored to the needs of individual patients is crucial for the optimum response to treatment with the goal of ameliorating symptoms, reducing disability and dependence on care givers, and enhancing quality of life.

Classification of hyperkinetic movement disorders

Before reviewing the treatment of hyperkinetic movement disorders, it is helpful to briefly define them and to describe their characteristic phenomenology.^{1,49} The discussion is organised according to the order of frequency in which the hyperkinetic movement disorders are encountered in a movement disorders clinic (table).

Tremor

Tremor is a rhythmical oscillatory movement of a body part.⁵⁰ Rest tremor is present when the affected body part is fully supported against gravity and not actively contracting; it is absent during complete rest, such as sleep. The presence of rest tremor suggests underlying nigrostriatal dopaminergic deficiency, as is the case in Parkinson's disease. Although rest tremors usually respond to levodopa therapy, some rest tremors, such as rubral tremor (also called Holmes' tremor; associated with lesions in the cerebellar-outflow pathways) or certain forms of essential and dystonic tremor, can occur even in the absence of parkinsonian features and their response to dopaminergic drugs is less predictable. Action tremor is present either during maintenance of a posture, such as when extending the arms horizontally and perpendicular to the body (postural tremor), typically seen in patients with essential tremor, or while moving the body part to and from a target (eg, finger to nose), which causes kinetic (intention) tremor. Although kinetic tremor can be present in patients with essential tremor, it is more typically seen in patients with cerebellar-outflow lesions. Unlike cerebellar tremor, patients with essential tremor, do not exhibit dysmetria or ataxia. Occasionally, tremor is seen only with certain specific actions or positions. Primary writing tremor is the most common type of task-specific tremor. Orthostatic tremor, an example of a position-specific tremor, is a less common and often unrecognised tremor, characterised by high-frequency (16 Hz) tremor, predominantly involving the legs and trunk when the patient stands for a certain

	n	Percentage*
Parkinsonism	9358	31.4
Parkinson's disease	6415	21.5
Dystonia	6037	20.2
Tremor (other than Parkinson's disease)	4529	15.2
Tics (including Tourette's syndrome)	2155	7.2
Chorea (including Huntington's disease)	900	3.0
Stereotypies (including tardive dyskinesia)	839	2.8
Restless legs syndrome	731	2.4
Myoclonus	626	2.2
Ataxia	360	1.2
Athetosis or ballism	77	0.3
Akathisia	67	0.2
Psychogenic	1588	5.3
Other	1218	4.3
Total	29 837	117.2

Data from 1977 to 2009. *Some patients have more than one movement disorder, hence the total percentage is more than 100.

Table: Frequency of movement disorders according to our clinical practice at the Baylor College of Medicine

period of time.⁵⁴ This tremor can also be present when the patient is in a supine position and presses their feet against a wall, and resolves during walking. Because of the high frequency of the tremor, it might not be readily visible, but can be easily detected by palpation, auscultation, or electromyography.

Dystonia

Dystonia is defined as a neurological disorder dominated by sustained muscle contractions, which frequently cause twisting, repetitive, and patterned movements or abnormal postures.⁵⁵ Dystonic movements can be slow, manifested by prolonged dystonic spasms resulting in abnormal postures, or can be rapid and jerk-like movements. Dystonia might also present as a rhythmical movement, most noticeable when the patient attempts to correct the underlying abnormal dystonic posture. This dystonic tremor can be abolished if the patient is asked to relax and allow the body part to move in the direction of the dystonic pull (null position). The adult-onset idiopathic dystonias, the most common dystonic disorders seen in neurological practice, are usually focal and remain focal or segmental. Examples include cranial dystonia (blepharospasm or oromandibular or lingual dystonia), cervical dystonia (spasmodic torticollis), laryngeal dystonia (spasmodic dysphonia), and dystonic writer's cramp. Dystonic writer's cramp is an example of a group of focal dystonias sometimes referred to as occupational spasms, which consist of task-specific or position-specific dystonias, such as musician's dystonias⁵⁶ and dystonias that affect athletes, artists, and other professions in which skilled movement is a key feature. By contrast with adult-onset dystonias, childhood-onset dystonias usually start distally and progress to a more generalised dystonia. Primary dystonias,

such as the autosomal-dominant dystonia caused by mutation in the gene that encodes torsin A (*TOR1A*; also known as *DYT1*),⁵⁵ are not associated with any other neurological disorders, whereas secondary dystonias might occur in Parkinson's disease or other forms of parkinsonism and various other neurological sporadic and genetic disorders.⁵⁷ Among the genetic disorders associated with dystonia and other hyperkinesias that are gaining increasing attention are syndromes of neurodegeneration with brain iron accumulation, which include pantothenate kinase-associated neurodegeneration (previously called Hallervorden–Spatz syndrome), neuroferritinopathy, infantile neuroaxonal dystrophy, aceruloplasminaemia, and *PLA2G6*-associated neurodegeneration (due to mutations in the gene that encodes phospholipase A2, group VI).^{58,59} Similar to copper chelation in Wilson's disease, iron chelators might be used in the future to treat these neurodegenerative disorders.⁶⁰

Tics and Tourette's syndrome

Tics are abrupt, usually brief, and often repetitive and stereotyped movements, which vary in intensity and are repeated at irregular intervals.⁶¹ The movements are most often jerky (clonic tics); however, slower, more prolonged movements (dystonic tics) or isometric muscle tensing (tonic tics) also occur. Tics can be present for several weeks or months, but many patients with childhood-onset tics develop Tourette's syndrome, a genetic disorder typically manifested by a wide array of chronic, fluctuating, simple, and complex motor and phonic (vocal) tics. Tourette's syndrome also has several associated comorbidities, such as attention-deficit disorder (with or without hyperactivity), obsessive-compulsive disorder, and impulse control disorder. Several other features are helpful in distinguishing this movement disorder from other dyskinesias. For example, patients usually have a generalised ("inner") urge that precedes the actual movement or a local feeling or discomfort in the region of the tic. These premonitory sensations are usually temporarily relieved by the occurrence of the tic.⁶² Tics are voluntarily suppressible for variable periods of time, but this usually occurs at the expense of mounting inner tension and an irresistible need to perform the tic, followed by a rebound burst of tics. By contrast with a common belief, motor and phonic tics can persist during all stages of sleep.⁶¹

Chorea and Huntington's disease

Chorea consists of irregular, purposeless, abrupt, rapid, brief, jerky, unsustained movements that flow randomly from one part of the body to another. The term "choreoathetosis" describes the combination of chorea and athetosis, a slow form of chorea manifested by writhing movements predominantly involving distal extremities. Ballism, a severe form of chorea, comprises wide amplitude, flinging movements, usually involves the proximal limbs and most often affects only one side

of the body (hemiballism). Ballism is typically caused by a lesion in the contralateral subthalamic nucleus, but might also be associated with pathology in other subcortical areas. Rarely, ballism can occur bilaterally (biballism or paraballism). Many patients with ballism also have distal choreic movements and, as recovery occurs, hemiballism often transforms into hemichorea and possibly even hemidystonia. Huntington's disease, an autosomal-dominant neurodegenerative disorder, is one of the most common causes of chorea, but other genetic causes include dentatorubral-pallidolusian atrophy, neuroacanthocytosis, benign hereditary chorea, spinocerebellar atrophies types 2, 3, and 17, neurodegeneration with brain iron accumulation, neuroferritinopathy, and ataxia telangiectasia. Non-genetic causes of chorea include cerebral palsy, systemic lupus erythematosus, Sydenham's chorea, chorea gravidarum, hyperthyroidism, vasculitis, antiphospholipid syndrome, Moyamoya disease, and several other drug-induced and metabolic disorders.⁶³

Stereotypy, akathisia, and tardive dyskinesia

Stereotypies are involuntary, patterned, repetitive, continuous, coordinated, purposeless, ritualistic movements, postures, or utterances. Stereotypic movements can be simple, as exemplified by a repetitive tongue protrusion, chewing, or body-rocking movements, or can be more complex, such as self-caressing, crossing and uncrossing of legs, marching in place, and pacing. Akathisia, which is usually of tardive origin, consists of the combination of complex stereotypic movements and an inner feeling of restlessness with inability to be still. As well as tardive dyskinesia (panel) caused by exposure to dopamine receptor-blocking drugs such as antipsychotics or antiemetics (eg, metoclopramide), other causes of stereotypies include mental retardation, autism, Rett syndrome, schizophrenia, and automatisms in patients with seizures.^{64,65}

Therapeutic options

Tremor

Medical therapy

Treatment of rest tremor associated with Parkinson's disease and associated parkinsonian disorders is not discussed in this Review, but treatment of essential tremor is, as it is the most common non-Parkinson's disease tremor encountered in clinical practice. As a first step in the treatment of essential tremor, exacerbating factors such as stress and various tremorgenic drugs should be minimised or eliminated. Although caffeine has not been convincingly shown to exacerbate essential tremor in specifically designed studies,⁶⁶ at the Movement Disorders Clinic, we advise our patients to limit their intake of caffeine-containing beverages. As alcohol reduces the amplitude of essential tremor in about two-thirds of patients, a glass of wine or alternative alcoholic drink (effective alcohol blood level can be as low

Panel: Recommended treatments of hyperkinetic movement disorders

Dystonia

Anticholinergic drugs, baclofen, botulinum toxin, globus pallidus internus DBS, repetitive transcranial magnetic stimulation²⁻¹¹

Hemifacial spasm

Botulinum toxin¹²

Tremors (essential tremor)

Propranolol, primidone, topiramate, botulinum toxin, ventral intermediate nucleus DBS¹³⁻¹⁸

Tics (Tourette's syndrome)

Fluphenazine, risperidone, botulinum toxin¹⁹⁻³²

Chorea (Huntington's disease)

Tetrabenazine³³⁻³⁶

Tardive dyskinesia

Withdrawal of the causative treatment, tetrabenazine (for tardive stereotypy, tardive chorea, tardive tremor), botulinum toxin (for tardive dystonia)³⁷⁻³⁹

Restless legs syndrome

Dopamine agonists (cabergoline, pramipexole, ropinirole, rotigotine), gabapentin, iron, levodopa, methadone, oxycodone⁴⁰⁻⁴⁵

Myoclonus

Clonazepam, levetiracetam, piracetam, sodium valproate^{46,47}

Painful legs and moving toes syndrome

Botulinum toxin, gabapentin, epidural spinal-cord stimulation⁴⁸

DBS=deep brain stimulation.

as 0.30%) can be offered as a prophylactic treatment—for example, before an important or stressful meeting or other occasion at which the presence of tremor could be a source of embarrassment. Many patients with essential tremor start consuming alcohol even before they become aware of their tremor and merely note that the alcohol calms their “nervousness”. The evidence concerning the risk of alcoholism among patients with essential tremor is contradictory, and some investigators have even suggested that alcohol is a risk factor for essential tremor.⁶⁷ Certainly, the regular use of alcohol to treat essential tremor is inadvisable. Alcohol is thought to act centrally, as infusion of alcohol into the brachial artery of a tremulous arm is ineffective in controlling the tremor. Alcohol is known to affect several neurotransmitters, and might stabilise neuronal membranes by potentiating GABA receptor-mediated chloride influx. A food additive, 1-octanol, suppresses harmaline-induced tremor in animal models of essential tremor and significantly decreases the amplitude of essential tremor for about 90 min.⁶⁸

Propranolol, a β -adrenergic blocker, and primidone, an anticonvulsant, remain the most effective drugs for the treatment of essential tremor. Propranolol is less effective for head and voice tremor than it is for hand tremor.⁶⁹ Although a central mechanism of action has been suggested for β -adrenergic blockers, some exert potent anti-tremor activity even though they are not lipid soluble and hence do not cross the blood–brain barrier. This suggests that the therapeutic effect of β -adrenergic blockers might be mediated, at least in part, by the peripheral β -adrenergic receptors. The major side-effects of propranolol and, to a lesser degree other β blockers, include fatigue, sedation, depression, and erectile dysfunction. β blockers are contraindicated in patients with asthma, second-degree atrioventricular block, and insulin-dependent diabetes.

The anti-tremor effect of primidone has been confirmed by several open trials and placebo-controlled studies.⁶⁹ By starting primidone at a low dose (≤ 25 mg at bedtime) and increasing this dose slowly over several weeks, the occasional acute, toxic side-effects (nausea, vomiting, sedation, confusion, and ataxia) can be prevented. Even starting primidone at such a low dose, however, does not always prevent idiosyncratic reactions. Side-effects can resolve even if primidone treatment is continued, but physicians should warn their patients of these possible reactions. Dosages of primidone of more than 250 mg per day are only rarely necessary. The anti-tremor effect of primidone is mostly attributed to the parent compound rather than to its metabolites, phenylethyl-malonamide or phenobarbital. In some patients, primidone might be more effective than propranolol, and a combination of the two drugs might be more efficacious than either drug alone.

In addition to β blockers and primidone, the benzodiazepine drugs, such as diazepam, lorazepam, clonazepam, alprazolam, and barbiturates might also have some ameliorating effects on essential tremor or its variants.⁷⁰ Mixed results from double-blind, placebo-controlled studies of gabapentin in essential tremor have been reported.¹³ However, topiramate was an effective anti-tremor drug in a multicentre, double-blind, placebo-controlled trial of 208 patients with essential tremor.⁷¹ In addition to a significant decrease in the Fahn–Tolosa–Marin tremor rating scale scores, topiramate was associated with a greater improvement in function and disability than did placebo. The most common adverse events were paraesthesias (58 [28%]), weight loss (46 [22%]), and taste perversion (40 [19%]); other side-effects included nausea, difficulties in concentration and attention, and somnolence. In a double-blind, placebo-controlled trial of 20 patients with essential tremor, the antiepileptic drug zonisamide, did not provide significant improvement in clinical rating scales, but did reduce tremor as measured by accelerometry.⁷² On the basis of a review of videos with investigators blinded to the treatment, a significant decrease in the amplitude of essential tremor with

zonisamide at a mean dose of about 250 mg per day was indicated; doses of more than 300 mg per day were associated with somnolence, poor energy, imbalance, and altered taste, without additional improvement in tremor.⁷³ Levetiracetam, another antiepileptic drug, had a significant anti-tremor effect in one double-blind, placebo-controlled trial at a single dose of 1000 mg,⁷⁴ but was not found to be effective in other studies.^{75,76} Pregabalin was effective in a pilot, double-blind, placebo-controlled trial,¹⁴ but another study did not show a significant benefit.⁷⁷ Other drugs reported to have a possible beneficial effect in patients with essential tremor include mirtazapine, clozapine, sodium oxybate, dimethoxymethyl-diphenyl-barbituric acid (also known as T2000), and carisbamate.⁷⁰ Drugs such as gabapentin, clonazepam, levodopa, primidone, phenobarbital, and amantadine might be effective in treating orthostatic tremor, but have not been tested in rigorously designed, controlled trials.

Botulinum toxin therapy

In patients with essential tremor who did not obtain adequate relief with oral medications, treatment with botulinum toxin might be considered. Injections of botulinum toxin into muscles that are involved in the production of the oscillatory movement, particularly the forearm wrist (and finger) flexors (eg, flexor carpi radialis and ulnaris) might provide a substantial decrease in the amplitude of the hand tremor for about 3 months, as suggested by data from two double-blind, placebo-controlled trials.^{15,16} Injections of botulinum toxin might be beneficial in patients with essential tremor involving the head⁷⁸ and voice.⁷⁹ Botulinum toxin might also be effective in primary writing tremor, although a specifically designed writing device might be a simpler treatment.⁸⁰

Surgical therapy

Finally, many studies have indicated beneficial effects for tremor produced by deep brain stimulation (DBS) targeting the ventral intermediate (Vim) nucleus of the thalamus⁸¹ and possibly other nuclei, such as the subthalamic nucleus^{82,83} and the caudal zona incerta nucleus.⁸⁴ Vim DBS mainly reduces contralateral, but to a lesser extent also ipsilateral, tremor,⁸⁵ as well as head tremor, rest and task-specific hand tremors,⁸⁶ and cerebellar-outflow tremors.⁸¹ Long-term studies, however, have found that bilateral Vim DBS is often associated with dysarthria, loss of balance, and loss of coordination.⁸⁷ Similar findings were reported in a 6-year follow-up of 38 patients with Parkinson's disease treated with Vim DBS in a multicentre European study.¹⁷ The authors suggested that unilateral Vim DBS should be reserved for elderly patients with Parkinson's disease who had predominant unilateral tremor. No meaningful benefit in essential tremor was shown in a multicentre trial of vagus nerve stimulation.¹⁸

The Quality Standards Subcommittee of the American Academy of Neurology reviewed the evidence of published trials in essential tremor and concluded that there was level A evidence that propranolol and primidone reduce limb tremor, but only level B evidence to support the effectiveness of alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate for reducing hand tremor, and of propranolol for reducing head tremor.⁶⁹ The effectiveness of the following treatments has received only level C support: clonazepam, clozapine, nadolol, and nimodipine, botulinum toxin in limb, head and voice tremor, and chronic DBS and thalamotomy. The main reason for the low level of support for botulinum toxin and DBS, despite their proven efficacy in reducing the amplitude of tremor, was the high occurrence of adverse events.

Dystonia

Medical therapy

The treatment of primary dystonia is only symptomatic, not neuroprotective, with the goal to relieve involuntary movements, correct abnormal posture, prevent contracture, reduce pain and embarrassment, and improve function.²³ A systematic review by a joint task force of the European Federation of Neurological Sciences and Movement Disorder Society concluded that “the absolute and comparative efficacy and tolerability of drugs in dystonia, including anticholinergic and antidopaminergic drugs, is poorly documented and no evidence-based recommendations can be made to guide prescribing”.⁴ A small number of patients have secondary dystonia with an identifiable aetiology and respond to specific treatments, such as levodopa in dopa-responsive dystonia, withdrawal of the causative treatment in drug-induced dystonia, or copper chelation in Wilson’s disease.

Before reviewing various pharmacological and surgical therapies, the role of education of patients and supportive care must be emphasised as these steps are integral components of a comprehensive approach to optimise treatment of patients with dystonia. Physical therapy and well fitted braces are designed primarily to improve posture and to prevent contractures. Although casting of the affected limb has been suggested as a potential treatment, such immobilisation can actually exacerbate or even precipitate dystonia, as is the case in peripherally induced dystonia.⁵¹ A variation of the immobilisation therapy, constraint-induced movement therapy, has been used successfully in rehabilitation of some patients with spasticity after stroke (attributed in part to cortical reorganisation), but whether this approach will have any use in the treatment of dystonia is unclear.⁵⁶ Another non-pharmacological treatment of dystonia involves the use of repetitive transcranial magnetic stimulation delivered at low frequencies (≤ 1 Hz) for 20 min, but this approach will be unlikely to gain wide acceptance.⁵

Although practising evidence-based medicine is a desirable goal, most recommendations of specific

treatments for different forms of dystonia are based on empirical observations rather than on data from randomised clinical trials. Therapeutic strategies must be tailored to the needs of individual patients and include chemodenervation with botulinum toxin injections in patients with focal or segmental dystonia, and pharmacological therapy or DBS in patients with generalised dystonia (figure 1).

Pharmacological treatment of dystonia is largely based on empirical, rather than scientific rationale. One exception is the dopa-responsive dystonia in which the biochemical and genetic mechanisms have been elucidated.⁶ Mutations in the gene that encodes GTP-cyclohydrolase 1 (*GCHI*) are an important genetic cause of dopa-responsive dystonia, but other genetic mutations, such as those in the genes that encode tyrosine hydroxylase (*TH*) and parkin (*PARK2*), might also be accountable for this dystonia. Dopa-responsive dystonia usually presents in childhood and the dystonia, postural instability, hypertonicity, and hyper-reflexia predominantly involving the legs is often wrongly attributed to cerebral palsy. Many patients with dopa-responsive dystonia have a family history of dystonia or Parkinson’s disease. At least half of the patients have diurnal fluctuations with notable progression of their symptoms towards the end of the day and a relief after sleep. Because dopa-responsive dystonia is not easily diagnosed, a therapeutic trial of levodopa is strongly recommended in all patients with childhood-onset dystonia because notable improvement in dystonia is the most reliable diagnostic test. Most patients with dopa-responsive dystonia improve notably even with small doses of levodopa (100 mg of levodopa plus 25 mg of a decarboxylase inhibitor), but some might require doses of levodopa as high as 1000 mg per day. By contrast with juvenile Parkinson’s disease, levodopa-induced fluctuations or dyskinesias are relatively rare in patients with dopa-responsive dystonia. In addition to levodopa, patients with dopa-responsive dystonia also improve with dopamine agonists and anticholinergic drugs.

Although antidopaminergic drugs might be beneficial in the treatment of dystonia, the potential clinical benefit is usually limited by the development of side-effects. However, dopamine-depleting drugs such as tetra-benzazine are useful in the treatment of some forms of dystonia, particularly tardive dystonia.³⁷

Anticholinergic medications are most beneficial in the treatment of generalised and segmental dystonia, as indicated in an early, double-blind, placebo-controlled trial.⁸⁸ This therapy is generally well tolerated when the dose is started low and increased slowly. We recommend starting with 1 mg of trihexyphenidyl and increasing the dose up to 12 mg per day over the next 4 weeks; but some patients might require up to 60–100 mg per day, although dose-related drowsiness, confusion, memory difficulty, blurring of vision, hallucinations, and urinary retention might limit its usefulness. These side-effects seem to be

more common in adults than in children, and can be managed by symptomatic therapies, such as pyridostigmine for constipation, pilocarpine eye drops for blurring of vision, cholinergic drugs such as bethanechol for urinary retention, and synthetic saliva for dry mouth.

In addition to anticholinergic drugs, other ancillary treatments used in patients with generalised dystonia include muscle relaxants such as benzodiazepines, tizanidine, cyclobenzaprine, and baclofen. Intrathecal baclofen infusion might be helpful to patients with truncal and leg dystonia, which are particularly associated with spasticity, such as that seen in cerebral palsy.^{89,90} Although reported to be helpful in some patients with dystonia associated with complex regional pain syndrome,⁹¹ the response is unpredictable and is associated with high complication rate, possibly as a result of associated psychogenic phenomenology in this group of patients. Other medications occasionally used in the treatment of dystonia include slow release morphine sulphate, sodium oxybate, levetiracetam, and zonisamide. Local electromyographically guided injections of phenol are only rarely used as the treatment is painful and the results are inconsistent.

Attacks of kinesigenic paroxysmal dystonia can be controlled with anticonvulsants (eg, carbamazepine, phenytoin, levetiracetam, topiramate).⁹² The non-kinesigenic forms of paroxysmal dystonia are less responsive to pharmacological therapy, although clonazepam and acetazolamide might be beneficial.⁹³ Patients with exercise-induced dystonia, which can overlap with epilepsy and has been associated with mutations in *SLC2A1* (which encodes the glucose transporter GLUT1), has been successfully treated with the ketogenic diet.⁹⁴

Rarely, dystonia can be so severe that not only are there abnormal postures, but also disabling dystonic movements compromising respiration and causing muscle breakdown, life-threatening hyperthermia, rhabdomyolysis, and myoglobinuria.⁹⁵ In a review of 37 cases of status dystonicus (also known as dystonic storm), the following treatment approach has been used with some success: early admission to the intensive care unit, monitoring for evidence of myoglobinuria, avoidance of respiratory and renal compromise, sedation with intravenous midazolam (initially up to 10 µg/kg/min and subsequently at 30–100 µg/kg/h), treatment with possible barbiturate anaesthesia combined with endotracheal intubation and mechanical ventilation, continuous intrathecal baclofen, and bilateral globus pallidus interna (GPI) DBS or pallidotomy.⁹⁵

Botulinum toxin therapy

The introduction of botulinum toxin into clinical practice in the late 1980s revolutionised the treatment of dystonia. Botulinum toxin is the most potent biological toxin and has become a powerful therapeutic tool in the treatment of several neurological, ophthalmic, oro-laryngeal, urological, autonomic, dermatological, and cosmetic disorders.⁷⁸

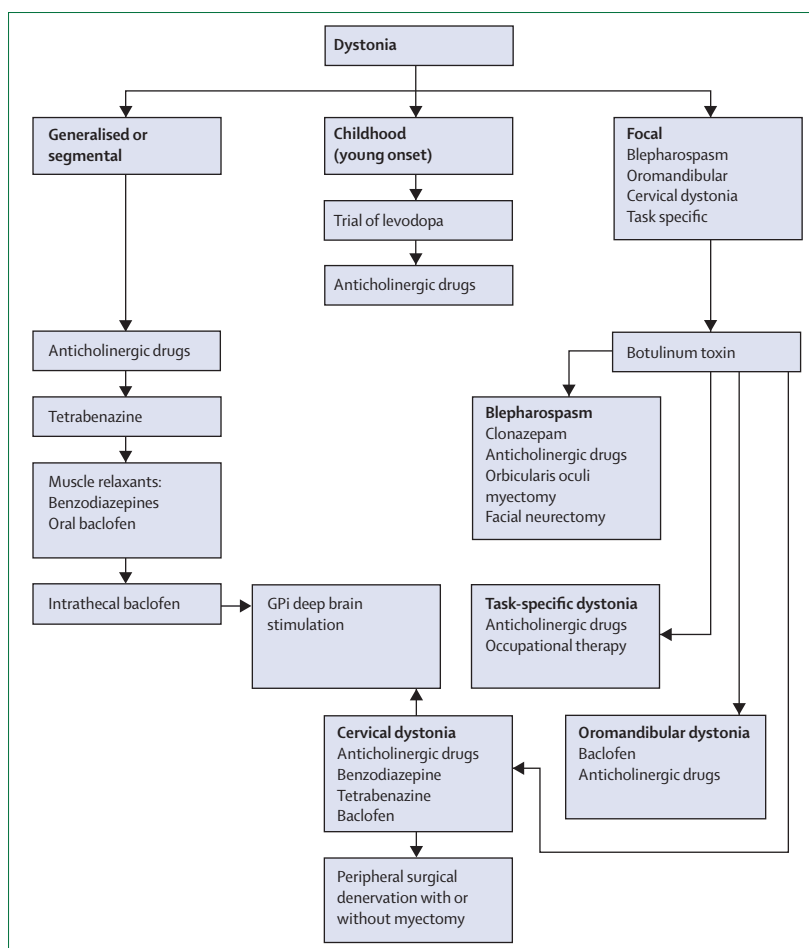


Figure 1: Therapeutic approaches for dystonia

This diagram outlines therapeutic approaches to patients with dystonia based on anatomic distribution and age at onset. The suggested treatments are listed in the order that they should be used if the prior approach is not successful. DBS=deep brain stimulation. GPI=globus pallidus internus.

Although botulinum toxin is currently used to treat more than a hundred different disorders, only a small percentage of the indications have been approved by regulatory agencies. In 1989, the US Food and Drug Administration (FDA) approved botulinum toxin A (Botox) as a therapeutic drug in patients with blepharospasm and other facial nerve disorders, including hemifacial spasm, and Botox and botulinum toxin B (Myobloc) in 2000 as treatments for cervical dystonia. In 2009, another botulinum toxin A, Dysport, was approved by the FDA for the treatment of cervical dystonia. The European Medicines Agency has already approved three botulinum toxin A preparations, Botox, Dysport, and Xeomin (NT-201), and one botulinum toxin B preparation, NeuroBloc, for the treatment of several dystonias and other therapeutic and cosmetic uses. These drugs have been also used in many countries of Latin and South America and Asia. The Chinese form of botulinum toxin A (Prosigne or CBTX-A) is similar in clinical efficacy and tolerability to Botox.⁹⁶ However, the biological activity, measured in units, is different for the

different products. The clinicians who use these products, therefore, must be knowledgeable about the properties and potencies of the various preparations, and they should recognise that the units are not interchangeable.

For more on the efficacy and safety of botulinum toxin in different indications, the reader is referred to some recent reviews.^{7,8} Although the various neurotoxins are antigenically different, they contain a common subunit structure and cross-reactive epitopes might cause cross-neutralisation of antibodies.⁹⁷ The risk of antibodies to Botox has markedly decreased from the original preparation on which most publications are based, and it is now estimated to occur in about 1–2% of patients receiving the product repeatedly for up to 4 years.^{98,99} Patients who develop blocking antibodies usually respond to an immunologically distinct botulinum toxin, although they still have an increased risk of developing antibodies to this second toxin and, therefore, are likely to develop resistance to the alternative type of botulinum toxin.¹⁰⁰

Based on evidence presented in published reports, the Therapeutics and Technology Assessment Committee of the American Academy of Neurology concluded that: botulinum toxin should be offered as a treatment option for cervical dystonia (level A evidence); can be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia, and upper extremity essential tremor (level B); and can be considered for hemifacial spasm, focal lower limb dystonia and motor tics (level C).⁹ However, absence of evidence to support specific treatment recommendation does not necessarily mean that botulinum toxin might not be effective for that particular indication. For example, on the basis of early, albeit not necessarily rigorously designed randomised clinical trials, the use of botulinum toxin for blepharospasm has been so well established in clinical practice as the treatment of choice that it would now be unethical to undertake additional placebo-controlled trials to further document the efficacy of botulinum toxin for this indication; hence, the recommendation has received only level B support. Another example is upper extremity essential tremor, which has also received only level B recommendation, despite a proven decrease in tremor amplitude. The recommendation was downgraded because of weakness in extensor finger muscles reported in the two placebo-controlled trials.^{15,16} We and other clinicians, however, have since modified the approach and no longer inject forearm extensor muscles, thus avoiding the extensor weakness, but the level B recommendation remains.

Surgical therapy

Patients who continue to experience troublesome or disabling symptoms from dystonia despite physical and pharmacological therapy and chemodenervation with botulinum toxin, might be candidates for surgical treatment. Improved understanding of the functional anatomy of the basal ganglia and physiological

mechanisms underlying movement disorders, coupled with refinements in imaging and surgical techniques, has led to a resurgence of surgery, particularly GPi DBS, as the treatment of choice for patients with disabling dystonia.^{101–103} Most studies have shown that patients with a phasic form of dystonia improved more than those with tonic contractions and posturing. The maximum benefit might not be achieved in some patients until 3–6 months after surgery. In a follow-up study of 22 patients, the 51% improvement in movement score observed at 1 year was maintained at 3 years (58%).¹⁰ In a study in several French centres, bilateral DBS of ventral GPi was associated with a 42% decrease in the Burke–Fahn–Marsden scale score; whereas DBS of dorsal GPi resulted in less predictable effects.¹¹ In addition to generalised dystonia, GPi DBS has also been effective in some patients with cervical dystonia¹⁰⁴ and cranial–cervical dystonia,¹⁰⁵ although patients with generalised dystonia seem to be better suited for stereotactic surgery than those with focal dystonia. Peripheral denervation procedures have been used extensively before the introduction of botulinum toxin, but are now used rarely and are usually restricted to cases with botulinum toxin-resistant blepharospasm or cervical dystonia.²

Tics

Medical therapy

The first step in the management of patients with Tourette's syndrome is proper education of the patients, relatives, teachers, and other individuals who frequently interact with the patient about the nature of tics and the various Tourette's syndrome comorbidities.^{19,20} Before deciding how to treat Tourette's syndrome-associated symptoms, it is important to decide whether to treat them. About 20% of patients referred to our Tourette's syndrome clinic do not need pharmacological therapy. Counselling and behavioural therapies, such as habit-reversal training,¹⁰⁶ might be sufficient for patients with mild symptoms or can be used as ancillary treatments to pharmacological therapy; however, continued compliance with behavioural therapies is a major limitation. The most troublesome symptoms should be targeted first. Medications should be instituted at low doses, titrated gradually to the lowest effective dosage, and tapered during less stressful periods (eg, summer vacations). Another important principle of therapy in Tourette's syndrome is that of giving each medication and dosage regimen an adequate trial.

Several controlled and open trials have found that, of the pharmacological drugs that are used for tic suppression, the neuroleptic drugs, which include the dopamine receptor-blocking drugs and monoamine-depleting drugs, are clearly most effective.²⁰ Of the various neuroleptic drugs, we prefer fluphenazine, as it seems to have a lower incidence of side-effects typically associated with neuroleptic drugs, such as sedation, depression, weight gain, and school phobia.¹⁹ Although tardive dyskinesia,

including tardive stereotypy and tardive dystonia, is a potential side-effect of fluphenazine, we have not encountered this complication in any of our patients (>1000) treated with this drug. In a double-blind, placebo-controlled, 8-week trial in which 24 patients were randomly assigned to risperidone in doses of 0.5 to 6.0 mg per day (median dose of 2.5 mg per day) and 24 patients were assigned to placebo, risperidone was significantly ($p < 0.05$) superior to placebo on the global severity rating of the Tourette's syndrome severity scale.¹⁰⁷ 15 patients in the risperidone group and six patients in the placebo group improved by at least one point on this seven-point scale. Fatigue and somnolence were the most common adverse events associated with risperidone. Despite some encouraging reports, based primarily on small or open-label trials,^{108,109} we have not found the atypical neuroleptics, such as aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone to be particularly effective in the treatment of tics. Furthermore, similar to pimozide, these drugs can prolong the QT interval and can be associated with other side-effects usually attributed to the classic neuroleptics, including tardive dyskinesia. Tetrabenazine, a monoamine-depleting drug, is a powerful anti-tic drug that has not been linked to tardive dyskinesia, and, as such, might be considered the first-line of treatment of patients with troublesome tics.²¹ Furthermore, tetrabenazine seems to be associated with less weight gain than the typical neuroleptics.¹¹⁰

Several non-neuroleptic drugs are effective in the treatment of tics. In a double-blind, placebo-controlled trial involving 29 patients with Tourette's syndrome, topiramate was found safe and effective for the treatment of moderately severe Tourette's syndrome.²² The findings that dopamine agonists improve tics seem paradoxical in view of the well known beneficial effects of anti-dopaminergic drugs. However, the observed effects of dopamine agonists could be mediated by their action on dopamine D2 autoreceptors, thus reducing endogenous dopamine turnover. Nevertheless, the preliminary reports^{23,24} are yet to be confirmed by randomised clinical trials. Pramipexole, a D2 and D3 receptor agonist, is being studied in a double-blind, placebo-controlled trial.^{111,112}

Other drugs effective in the treatment of tics are clonazepam, flutamide (an acetanilid non-steroidal androgen antagonist), ondansetron, baclofen, donepezil, nicotine, and cannabinoids, but rigorously designed studies of these drugs are lacking.

Discussion of the treatment of Tourette's syndrome comorbidities, such as attention-deficit hyperactivity disorder, obsessive-compulsive disorder, impulse control disorder, and other behavioural disorders, is beyond the scope of this Review.¹⁹ In addition to the CNS stimulants used in the treatment of attention-deficit hyperactivity disorder, atomoxetine, modafinil, and armodafinil, we often use guanfacine and clonidine to treat behavioural comorbidities, particularly impulse-control problems.

Although clonidine is often used to treat tics in children, we do not find this presynaptic α_2 -adrenergic agonist a particularly effective anti-tic drug.

Botulinum toxin therapy

Localised motor tics can be successfully treated with botulinum toxin injections in the affected muscles.^{25,26} Such focal chemodenervation ameliorates not only the involuntary movements and vocalisations (including coprolalia), but also the premonitory sensory component. Botulinum toxin has been also used to control some life-threatening tics, such as dystonic cervical tics ("whiplash" tics) that otherwise could cause compressive myelopathy or radiculopathy.^{27,28}

Surgical therapy

Surgical treatment of Tourette's syndrome has emerged as an effective intervention in patients with disabling (malignant) Tourette's syndrome, particularly if associated with self-injurious behaviours.²⁷ An increasing number of reports have provided evidence that DBS targeting thalamus, globus pallidus and other brain regions might be an effective strategy to treat uncontrollable and potentially life-threatening tics,²⁹⁻³² and the associated obsessive-compulsive disorder.¹¹³

Chorea

Medical therapy

Most studies on the treatment of chorea were undertaken in patients with Huntington's disease (figure 2). Because of increased understanding of mechanisms of neurodegeneration, the availability of suitable animal models, and of pre-symptomatic testing, Huntington's disease is an excellent model for evaluating early neuroprotective treatments.^{114,115} Despite these advances, however, there is currently no treatment that stops or slows the progression of Huntington's disease, but the following treatment approaches are being investigated in clinical trials designed to indicate potential disease-modifying effects: coenzyme Q10, creatine, dimebon, ethyl eicosapentaenoate (Miraxion), and minocycline.^{114,115}

When chorea is mild and not troublesome, treatment is not needed even though family members might demand some therapeutic intervention, just for cosmetic purposes. Although dopamine receptor-blocking drugs (neuroleptics) have been used in the past as the main treatment of chorea, the usefulness of these drugs is limited by potentially serious side-effects, including parkinsonism and tardive dyskinesia. In an evidence-based review of 218 publications on pharmacological interventions in Huntington's disease between 1965 and 2005, there were 20 papers with level I trials, 55 with level II trials, and 54 with level III trials, and 89 case reports.¹¹⁶ Chorea, the primary target symptom in nearly all studies, improved with haloperidol and fluphenazine, with less evidence for olanzapine. Amantadine has a

variable effect on Huntington's disease-associated chorea;¹¹⁷ a double-blind, randomised crossover study showed a decrease in dyskinesia scores after both intravenous and oral administration of amantadine.¹¹⁸

Introduced for the treatment of chorea in the UK in 1971, tetrabenazine was not readily available in the USA until 2008, at which time the FDA approved tetrabenazine (Xenazine; also marketed as Nitoman) as the first drug for the treatment of chorea associated with Huntington's disease. A potent and selective depletor of dopamine from nerve terminals, and, to a lesser extent norepinephrine and serotonin, tetrabenazine is effective in the treatment of several hyperkinetic movement

disorders.³⁷ By inhibiting the brain synaptic vesicular monoamine transporter type 2 (VMAT2), tetrabenazine impairs uptake of monoamines into synaptic vesicles, causing them to remain in the cytoplasm, where they are rapidly degraded by monoamine oxidases. In human beings, VMAT2 is nearly exclusively expressed in CNS neurons, whereas VMAT1 is present in peripheral nerve terminals. Tetrabenazine mainly inhibits VMAT2, whereas reserpine, an old antihypertensive drug, binds irreversibly to both VMAT1 (peripheral) and VMAT2 (central). These pharmacological differences probably account for the absence of hypotension and gastrointestinal side-effects with tetrabenazine compared with reserpine. The weak dopamine D2 receptor antagonism is unlikely to be involved in the therapeutic effect of tetrabenazine, which might be one reason why tardive dyskinesia has not been documented to be caused by tetrabenazine. Although tetrabenazine can cause or exacerbate depression, sedation, akathisia, and parkinsonism, this drug is an effective anti-chorea drug and has the advantage over the other neuroleptics in that it does not seem to cause tardive dyskinesia.^{33,119,120} In a multicentre, double-blind, placebo-controlled trial (TETRA-HD) involving 84 ambulatory patients with Huntington's disease (54 receiving tetrabenazine, 30 receiving placebo), tetrabenazine decreased chorea severity by a mean of 5.0 units on the unified Huntington disease rating scale (UHDRS) compared with a mean decrease of 1.5 units with placebo treatment (adjusted mean effect size of -3.5 ± 0.8 units, $p < 0.0001$).³⁴ Ratings of clinical global impression also significantly improved. There were five study withdrawals in the tetrabenazine group and five serious adverse events in four subjects (drowning suicide, complicated fall, restlessness or suicidal ideation, and breast cancer), compared with one withdrawal and no serious adverse events in the placebo group. In the FDA application for approval of tetrabenazine in Huntington's disease, the findings from this controlled, prospective study were supplemented by data obtained from an observational, longitudinal study at Baylor College of Medicine (under an Investigational Exemption for a New Drug for the author).³⁷ In this study, 448 patients with hyperkinetic movement disorders (98 with chorea) treated with tetrabenazine (mean dose at the last visit 60.4 ± 35.7 mg) for up to 21.6 years (mean 2.3 ± 3.4 years) between 1997 and 2004, were evaluated with a clinical response scale (1=marked reduction in abnormal movements; 5=worsening). The percentage of patients with chorea with a response rated as 1 or 2 at the last visit was 84.4%. The most common side-effects, all related to dose, were drowsiness in 112 patients (25%), parkinsonism in 69 patients (15.4%), depression in 34 patients (7.6%), and akathisia in 34 patients (7.6%), with less common side-effects including nausea or vomiting, nervousness or anxiety, and insomnia. Many patients are willing to tolerate side-effects such as parkinsonism (sometimes effectively treated with

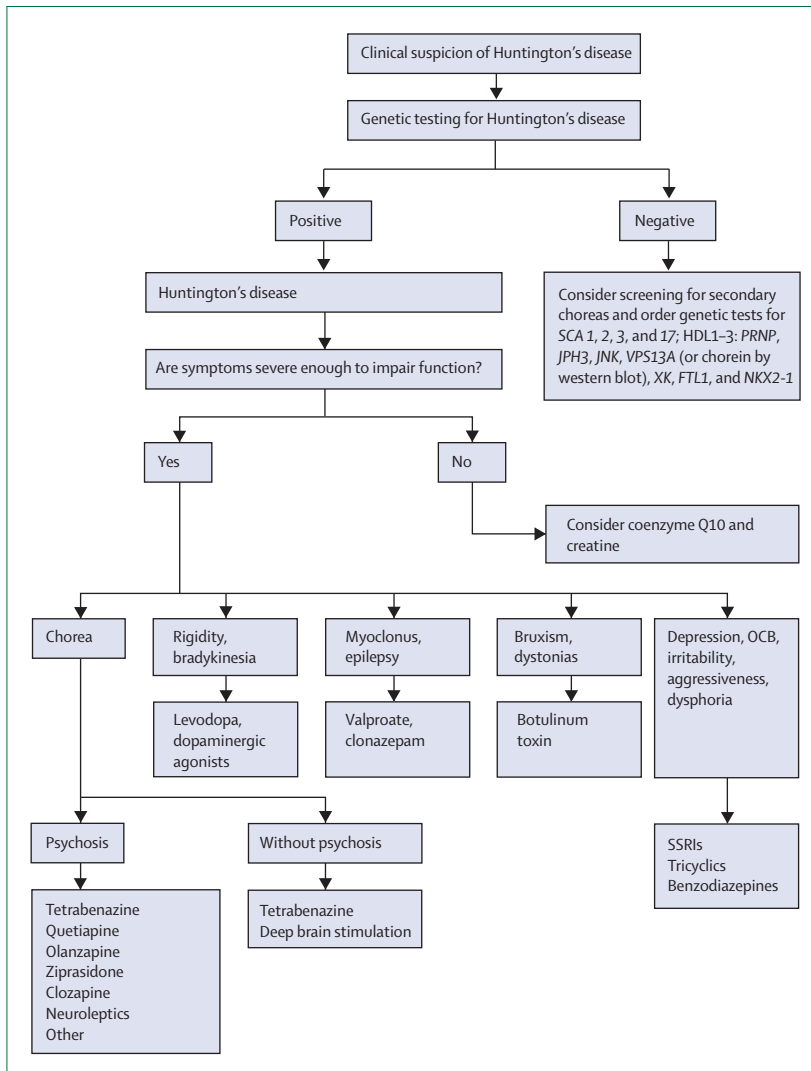


Figure 2: Therapeutic approaches for the treatment of Huntington's disease
 Therapeutic approaches for patients with Huntington's disease based on clinical manifestations. *FTL1*=gene for ferritin light chain (mutated in neuroferritinopathy). *HDL*=Huntington's disease-like. *JNK*=gene for c-Jun NH-terminal kinase gene (mutated in DRPLA). *JPH3*=gene for junctophilin 3. *NKX2-1*=gene for NK2 homeobox 1 (also known as *TITF1*; mutated in benign hereditary chorea). *OCB*=obsessive-compulsive behaviour. *PRNP*=gene for prion protein (mutated in HDL1). *SCA*=spinal-cerebellar ataxia. *SSRI*=selective serotonin re-uptake inhibitor. *VPS13A*=gene for vacuolar protein sorting 13 homolog A (mutated in neuroacanthocytosis). *XK*=gene for X-linked Kx blood group (mutated in McLeod's syndrome).

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “tremors”, “dystonia”, “chorea”, “tics”, “myoclonus”, “botulinum toxin”, and “tetrabenazine”, from 1980 to May, 2009. Articles were also identified through searches of the author’s own files. Only papers published in English were reviewed. Books on movement disorders published during the same period, personal experience and judgment, and comments from the reviewers were also used in preparation of this paper.

amantadine, levodopa, and dopamine agonists) because of tetrabenazine’s beneficial effects on their hyperkinetic movement disorder. This effect is also supported by another double-blind study undertaken at Baylor College of Medicine in which re-emergence of chorea was shown when 30 patients with Huntington’s disease treated with a stable dose of tetrabenazine were randomly assigned to a staged withdrawal.³⁵ The observations of tetrabenazine’s beneficial effects on chorea have been supported by other, albeit smaller, longitudinal studies including one in which 68 patients with Huntington’s disease were followed for a mean period of 34.4±25.2 months.³⁶ Physicians must be educated about the pharmacology and use of tetrabenazine, including the need for slow, careful dose titration and monitoring for depression or suicidality and other potential adverse events such as sedation, parkinsonism, and akathisia. The dosage should be periodically reduced to determine whether continued treatment is necessary. Although cytochrome (CYP2D6) genotyping has been recommended by the FDA for doses more than 50 mg per day, most clinicians will probably continue to be guided by their clinical judgment, rather than by costly genotyping, to determine whether patients metabolise drugs quickly or not.

Surgical therapy

Palliative surgery, including pallidotomy and DBS, has been investigated in a few patients with severe chorea associated with Huntington’s disease. Low-frequency (40 Hz) GPi DBS was associated with reduced chorea, but the overall motor function and quality of life did not improve.¹²¹ Whether fetal cells or intrastriatal implantations of genetically engineered cells designed to produce trophic factors will be useful in the treatment of Huntington’s disease awaits the results of further animal and clinical studies.^{122,123} Finally, RNA interference has been suggested as a promising therapeutic strategy, but further work is needed to determine whether this method can suppress the expression of only the mutated, but not the normal gene that encodes the huntingtin protein.¹²⁴

Unanswered issues and concluding remarks

Although progress is being made in our scientific knowledge and symptomatic treatment of movement

disorders, we are still lacking pathogenesis-targeted therapies. Development of such therapeutic strategies for hyperkinetic movement disorders will require better understanding of the pathophysiological mechanisms, clear and testable hypotheses, proof-of-principle and pilot studies, well designed randomised, controlled trials, and long-term observational trials. Although therapeutic decisions should be evidence-based, data generated by placebo-controlled trials, which are often short-term and limited by strict inclusion-exclusion criteria and other protocol restrictions, might not always apply to individual patients. Clinicians must, therefore, not only rely on scientific evidence but also use their own experience and best clinical judgment when selecting the optimum therapeutic strategy—a fundamental principle in care of patients. Translating this growing body of knowledge from the bench and from sophisticated statistical analyses to a patient-oriented clinic practice continues to be an important unmet need not only in the therapeutics of movement disorders, but in medicine in general.

Conflicts of interest

I have received research grants from Advanced Neuromodulation Systems, Allergan, Boehringer-Ingelheim, Ipsen, Medtronic, Merz Pharmaceuticals, National Institutes of Health, National Parkinson Foundation, Novartis, Ortho-McNeil, Teva, and the Parkinson Study Group. I have served as a consultant for Allergan, Ipsen, Merz Pharmaceuticals, Ovation Pharmaceuticals, Teva, and Medlink Neurology.

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