Treatment of dystonia

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Dystonia may be a sign or symptom, that is comprised of complex abnormal and dynamic movements of different etiologies. A specific cause is identified in approximately 28% of patients, which only occasionally results in specific treatment. In most cases, treatment is symptomatic and designed to relieve involuntary movements, improve posture and function and reduce associated pain. Therapeutic options are dictated by clinical assessment of the topography of dystonia, severity of abnormal movements, functional impairment and progression of disease and consists of pharmacological, surgical and supportive approaches. Several advances have been made in treatment with newer medications, availability of different forms of botulinum toxin and globus pallidus deep brain stimulation (DBS). For patients with childhood-onset dystonia, the majority of whom later develop generalized dystonia, oral medication is the mainstay of therapy. Recently, DBS has emerged as an effective alternative therapy. Botulinum toxin is usually the treatment of choice for those with adult-onset primary dystonia in which dystonia usually remains focal. In patients with secondary dystonia, treatment is challenging and efficacy is typically incomplete and partially limited by side effects. Despite these treatment options, many patients with dystonia experience only partial benefit and continue to suffer significant disability. Therefore, more research is needed to better understand the underlying cause and pathophysiology of dystonia and to explore newer medications and surgical techniques for its treatment.

The term dystonia was first used by Oppenheim in 1911 to describe a childhood-onset disorder, characterized by twisted postures, muscle spasms, bizarre walking with bending, twisting of the torso and development of sustained, fixed postural deformities that was known for decades as ‘dystonia musculorum deformans and dystonia lordotica progressiva’ [1]. Later that year, Flatau and Sterling suggested the inherited nature of the disorder [2]. Over time, dystonia had different meanings until an ad hoc committee of the Dystonia Medical Research Foundation clarified its definition as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [3]. In addition, the term torsion is often used to emphasize the twisting quality of the abnormal movements, which distinguishes dystonic movements from those of chorea, rigidity, stiffness and neuromyotonia.

The hallmark of dystonia is the cocontraction of agonist and antagonist muscles owing to a failure of normal reciprocal inhibition, with overflow or spread into other regions [4]. Dystonic movements are often aggravated by purposeful actions and, stress and may be task-specific; for example, a patient may experience dystonia only when using a hand for writing, but not eating (writer’s cramp). As dystonia progresses, it may become activated by movements in body parts other than the involved area. In advanced cases, the dystonic posturing is evident even at rest. Recent studies have suggested several pathophysiological mechanisms, including abnormal reciprocal inhibition in the brainstem and spinal cord,
faulty sensorimotor feedback and integration and pallidal underactivity, with overactive thalamocortical projections [4,5]. Sensory input can overcome dystonic postures, exemplified by the sensory trick or geste antagoniste, a maneuver or position in which cutaneous stimulation at a particular site can significantly diminish the severity of dystonia in some patients [6].

The term dystonia describes a symptom or sign. In addition, the clinical spectrum of dystonia is remarkably variable and the dystonic syndromes are now considered as a heterogeneous disorder, comprising a vast array of diseases. At least three schemes have been proposed for classification, including the age at onset, the distribution of affected body regions and etiologically, as primary, dystonia-plus, heredodegenerative dystonias, post-traumatic, toxic and secondary dystonias. Marsden and colleagues emphasized the age at onset as the single most important feature in determining outcome; the earlier the age at onset, the more likely symptoms will be severe, with dystonia spreading to involve multiple regions [7]. Subsequent analysis of the distribution of ages at onset in a clinically ascertained population further confirmed a bimodal distribution (with modes at 9 and 45 and a nadir at 27 years) [8]. When primary dystonia begins in childhood or adolescence, it often starts in a leg or arm and then progresses to involve multiple body regions; when it begins in adults, symptoms first involve the neck, cranial or arm muscles and dystonia tends to remain localized [9]. Furthermore, early-onset primary dystonia has a genetic background in the great majority of cases. Although establishing separate groups for age at onset and distribution is helpful clinically, it does not fully explain the complex relationship between age at onset, muscles involved, progression and, importantly, the cause. While the definition of secondary or symptomatic dystonia seems to be straightforward, including a group of dystonic syndromes of identifiable etiologies, often accompanied by other neurological deficits, the scope of idiopathic dystonia is consistently changing, now comprising a group of clinical syndromes that are likely to have a genetic basis [10-12]. Therefore, the term primary torsion dystonia (PTD) has been proposed to replace idiopathic dystonia and the following clinical criteria should be met, including dystonia as the sole abnormality directly attributable to the condition, no laboratory or imaging abnormalities, as well as no dramatic response to levodopa, and no history of a known acquired or environmental cause of dystonia, for example, neuroleptic exposure [11]. Dystonia-plus represents a group of dystonic syndromes of possible neurochemical disorders, without evidence of neurodegeneration, associated with other characteristic clinical signs other than dystonia, for example, parkinsonism in dopa-responsive dystonia (DRD) and rapid-onset dystonia parkinsonism (RDP) and myoclonus in myoclonus-dystonia (M-D) [10]. Lastly, heredodegenerative dystonia includes a group of neurodegenerative diseases in which dystonia is sometimes a prominent feature. They generally present with other neurological symptoms besides dystonia.

Currently, several therapeutic options are available for the management of dystonia, including pharmacological therapy, botulinum toxin injections, stereotactic surgery and physical and behavioral modification techniques. While botulinum toxin (BTX) and functional neurosurgery have gained popularity in recent years for the treatment of both generalized and focal dystonia, medical therapy still plays a significant role, particularly for alleviation of pain and dystonic spasms. With the exception of DRD, Wilson’s disease, biotin deficiency and brain tumors, where specific therapies are available, the treatment of dystonia is largely symptomatic with the goal of reducing pain, decreasing abnormal movements, preventing contractions and restoring functional abilities, while minimizing side effects of the treatment. The selection of a therapy is partly guided by personal clinical experience and empirical trials, but the patient’s age, the anatomical distribution of the dystonia and the potential risk of adverse effects are also important determinants of the choice of therapy. Identification of a specific cause of dystonia, such as DRD, Wilson’s disease or drug-induced dystonia, may lead to a treatment targeted to the particular etiology. Therefore, it is prudent to search for the cause of dystonia, particularly when atypical features are present. For patients with early-onset PTD, most of whom have segmental or generalized dystonia, oral medication is usually the mainstay of therapy. For those with adult-onset PTD, in which the dystonia tends to be focal, botulinum toxin therapy is generally considered to be the treatment of choice. The management of dystonia can be very difficult. Patients may not respond to one type of therapy and multiple strategies may be necessary before an effective therapy can be found. When the above treatments fail, surgical therapies, including peripheral procedures and deep brain stimulation (DBS) may be considered. Symptomatic or secondary dystonias tend to respond less well to pharmacotherapy. In some patients, dystonia can be so severe, termed ‘dystonic storm or status dystonicus’, that it may compromise respiration or result in rhabdomyolysis and myoglobulinuria in which appropriate interventions can be life saving [13].

A variety of instruments has been developed to assess the response to treatment in patients with dystonia. For quantitative assessment of dystonia, a rating scale should comprise at least two sections: a movement scale, based on examination, and a disability scale, based on the patient's statement regarding activities of daily living (ADL) [14]. To be valid, increasing scores should correlate with both clinical impressions of the severity of dystonia and with increasing disability of ADL. To be reliable, the same examiner should obtain the same score at different times (intra-rater reliability) and different examiners of the same patient should also obtain similar scores (inter-rater reliability). Among different scales for focal dystonias, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is being used and validated most frequently [15,16]. The TWSTRS (range 0–87) consists of three subscales: severity (range 0–35), disability (0–23) and pain (0–20). The Burke-Fahn-Marsden scale (BFMS) and the Unified Dystonia Rating Scale (UDRS) are the two most frequently used scales in
patients with generalized dystonia [17,18]. Other scales include the visual analog scale (VAS) global assessment of change and pain analog assessments, but these are used less commonly in clinical trials in dystonia [14,17,18].

Pharmacological therapy
A large number of drugs with a variety of pharmacological actions have been reported to ameliorate dystonia. These medications include anticholinergics, dopaminergics, benzodiazepines, dopamine depletors, dopamine antagonists and other miscellaneous agents. However, most of these reports are anecdotal and the efficacy of these drugs is difficult to assess for several reasons: trials have often been conducted in small samples of patients; there are limited available data from double-blind, placebo-controlled studies and the spontaneous evolution of the dystonia with occasional transient remissions may interfere with clinical results of the trials. Furthermore, a large placebo effect has been demonstrated in clinical trials of dystonia [19]. Therefore, medical strategies are usually based on anecdotal and personal experience together with empirical use over many years, rather than evidence-based scientific data [20,21].

Since then, there have been a number of fairly large clinical trials. In addition, enough experience has accumulated concerning some drugs to summarize these findings and to draw general conclusions. In general, when initiating an oral medication, the key is to start at a low dose, slowly titrate to minimize side effects and to use the lowest effective dose. All drugs should be given in divided doses throughout the day. It is also important to reassure patients of a possible delayed response and that they need to be patient while awaiting this.

Medical therapy of dystonia may be discussed in terms of therapy for specific focal dystonias, such as blepharospasm, cervical dystonia or writer’s cramp, varieties of segmental dystonia or generalized dystonia. However, there is insufficient evidence to determine whether pharmacological differences exist among the various focal, segmental and generalized dystonias. Therefore, this review considers pharmacotherapy of all types of dystonia, organized by drug class.

Dopaminergic therapy
In contrast to Parkinson’s disease (PD), in which therapy with levodopa is based on the known depletion of dopamine in the brains of parkinsonian animals and humans, current knowledge of biochemical alterations in idiopathic dystonia is lacking. An important exception is DRD, where biochemical and genetic mechanisms have been demonstrated in several postmortem, molecular DNA and biochemical studies. DRD is usually a childhood-onset dystonia, characterized by dystonia of the lower limbs, which commonly evolves into generalized dystonia, sometimes associated with parkinsonism, diurnal variations with worsening toward the evening and female predominance [22]. Nygaard and colleagues estimated that 5–10% of patients with childhood-onset dystonia have DRD [23]. DRD is a true biochemical disorder and, in most cases, it is caused by a mutation in the guanosine triphosphate (GTP) cyclohydrolase I gene on chromosome 14q, which indirectly regulates the production of tetrahydrobiopterin, a cofactor of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine [24]. More recently, other mutations, such as involving tyrosine hydroxylase as well as autosomal recessive forms have been reported [25,26]. There is insufficient dopamine owing to low levels of converting enzyme in the heterozygous carriers. There is no evidence of nigrostriatal neurodegeneration [24,27]. Therefore, patients with DRD typically exhibit dramatic responses to levodopa within days to a few weeks, even with relatively small doses of levodopa, such as 100 mg of levodopa with 25 mg of decarboxylase inhibitor three times daily. Many patients return to nearly or completely normal functional levels. In some surveys, the daily dosage of levodopa has been 100–3000 mg/day, with an average of 500–1000 mg/day [23].

In the usual clinical setting, a trial of levodopa with doses of up to 600 mg/day is the most useful method for diagnosis in DRD as it provides rapid and dramatic improvement with nearly complete elimination of symptoms. The benefits are usually sustained in typical cases [28–30]. However, a frequent error is to expect an immediate and dramatic response in every patient with DRD as the response is sometimes moderate in adults when symptoms have been longstanding or in patients with compound heterozygous mutations. Moreover, progressive improvement can continue to occur over several years. Therefore, it is important that patients with suspected DRD continued on a sufficiently high dose of levodopa for a reasonable period of time. Some authors recommend that a sufficient trial in adults should include 400 mg/day of levodopa/carbidopa for the first 4 weeks and 600 mg/day for the next 4 weeks [31]. In children, the starting dose should be 1 mg/kg [31]. Although a dramatic response to levodopa supports the diagnosis of DRD, this test cannot distinguish DRD from early-onset parkinsonism owing to parkin mutations in which a dramatic response may also occur. The absence of marked levodopa-induced dyskinesias and motor fluctuations after sustained treatment eventually differentiates DRD from dystonia due to a parkin mutation [32,33]. This difference is explained by the absence of dopaminergic cell loss in the substantia nigra in DRD, as opposed to parkin mutations, which cause marked dopaminergic cell loss in the substantia nigra. Occasionally, high doses of levodopa can produce dyskinesias in DRD; while not dangerous, this can be frightening to patients and families [34].

Because of the dramatic response to levodopa and the varied phenotypes in DRD, including focal and more generalized dystonia, parkinsonism, and spastic paraplegia, a therapeutic trial of levodopa should be considered in all patients with childhood-onset dystonia, with or without classic features of DRD [35,36]. Patients with DRD may also respond to low-dose anticholinergic drugs and dopamine agonists [29,37]. Tetrahydrobiopterin, a cofactor for hydroxylation of tyrosine, has been shown to have a mild-to-moderate effect in patients with progressive dystonia and diurnal variation in two uncontrolled studies [38,39]. In general, if no clinically evident
improvement is observed after 1–3 months of levodopa therapy, DRD is probably not present and alternative medications should be considered.

Some patients with idiopathic or symptomatic dystonia, which is not of the DRD phenotype, may also respond to levodopa, but usually at higher doses than those required for DRD. However, early uncontrolled attempts to treat generalized dystonia with levodopa reached contradictory conclusions [40]. Some studies reported improvement in dystonia, while others found that levodopa may exacerbate dystonia [41–44]. Interpretation of early studies of dopaminergic agents in dystonia is complicated because, at that time, DRD was not distinguished from other forms of idiopathic dystonia. In addition, dopamine agonists used in some studies may have other pharmacological properties [45,46]. In a large review of dopaminergic agents in the treatment of generalized and focal dystonia, an attempt was made to exclude cases with diurnal variation and parkinsonism which may have had DRD [44]. It appeared that approximately 35% of patients with generalized dystonia improved with levodopa in open trials, but the improvement was rarely dramatic [44]. In addition, 19% of patients become worse. Open trials with apomorphine, bromocriptine and lisuride in small numbers of patients with focal and generalized dystonia, also did not yield dramatic benefit [47–50]. In conclusion, after excluding patients with diurnal dystonia, a trial and error approach has been suggested for the use of dopaminergics in treating dystonia [44]. Greene and colleagues reported that many patients who failed previous trials of levodopa responded to anticholinergic therapy [42]. Thus, although there is no head-to-head comparison between anticholinergic drugs and dopaminergic agents, it appears that a lower percentage of patients respond favorably to dopaminergic than to anticholinergic drugs.

Most patients with dystonia tolerate dopaminergic agents well. Major side effects are uncommon but include nausea, light-headedness, sedation, confusion or visual hallucinations. In cases where there is worsening of dystonia with dopaminergic agents, this increase in symptoms will resolve when the medications are discontinued.

**Anticholinergic drugs**

Anticholinergic drugs have been found to be the most useful medication for the treatment of generalized and segmental dystonia [42,51,52]. Fahn was the first to report that high-dose anticholinergic therapy was beneficial in patients with dystonia [53,54]. Since then, other studies have replicated these results in both open-label and controlled, double-blind trials [18,42,43,55–57]. Trihexyphenidyl is the only anticholinergic agent demonstrated to be effective in a double-blind, randomized, placebo-controlled trial for the symptomatic treatment of segmental and generalized dystonia in young patients but not in adults [18,40]. These studies all demonstrated that approximately 50% of children and 40% of adults with idiopathic dystonia obtain a moderate-to-dramatic benefit from this drug. A total of 31% of patients with secondary dystonia, including those with dystonia after birth injury and tardive dystonia, also had a good response to anticholinergics, which was not different from the response rate of all patients with primary dystonia [43,58]. The best clinical effect was achieved when treatment was initiated within 5 years of symptom onset [42,54]. In general, children enjoy more frequent and dramatic improvement with fewer side effects than adults. However, there are no good controlled studies demonstrating the efficacy of anticholinergics in adults. The difference between response rates in children and adults may be due, at least in part, to the ability of children to tolerate much higher doses of these agents. Dose-limiting side effects with anticholinergic agents are their peripheral and central adverse effects. Peripheral side effects, such as dry mouth and blurred vision, are common. These symptoms can be ameliorated by co-administration of a peripherally acting anticholinesterase, such as pyridostigmine, synthetic saliva and eye drops of pilocarpine, a muscarinic agonist. By contrast, central side effects, such as forgetfulness, visual hallucinations, confusion and behavioral changes, usually require that the anticholinergic dose is reduced, which lessens the usefulness of these agents [59]. Despite these acute adverse effects, no long-term sequelae have been reported.

Although the efficacy of anticholinergic agents is now established and they are probably the most common systemic agents used in the treatment of dystonia, their mechanism of action remains unknown [43]. Trihexyphenidyl and benztropine are the two most commonly used anticholinergic agents. The mechanism of action of trihexyphenidyl is probably a central antimuscarinic effect. Benztropine has anticholinergic and antihistaminic effects and also blocks presynaptic dopamine uptake. Anticholinergic therapy is better tolerated if the dose is increased slowly. Rapid dose escalation can lead to confusion. The improvement can be delayed for several weeks. For trihexyphenidyl, treatment should be started at 1 mg/day at bedtime and increased by 2 mg/week up to the maximum tolerated dose. Other slow titration regimens can be used to avoid side effects. In one study, the average daily dose achieved was 41 mg/day, with a dosage range of 8–80 mg/day [42]. Some patients may require up to 120 mg/day, but may experience dose-related drowsiness, confusion or memory difficulty. Although most patients require high doses of anticholinergics before improvement occurs, the anticholinergic dose should be kept as low as possible so as to maintain physical independence, rather than increasing the dose to its limits in the hope of abolishing all dystonic spasms. Paradoxical worsening of symptoms with anticholinergics is rarely observed although some patients worsen at a low dose, followed by improvement at higher doses [54].

**Baclofen**

Baclofen is a derivative of γ amino butyric acid (GABA) that reduces spinal cord interneuron and motor neuron excitability, possibly via activation of the presynaptic GABA<sub>B</sub> receptors [60]. While several actions at many sites in the nervous system have been described, the exact mechanism by which baclofen affects dystonia is still unknown, but may be
related to its activity as a GABA agonist at the spinal cord, basal ganglia and cortical levels [61,62]. There have been no controlled studies of baclofen in the treatment of dystonia, but it has been shown to be effective in a number of case reports and retrospective trials, particularly in children and adolescents [63–65]. Significant improvement in dystonic symptoms, especially gait, was found in 30% of 31 children with primary idiopathic dystonia at doses ranging from 40 to 180 mg daily [65]. In this trial, the average daily dose of baclofen in clinically responsive patients was 79 mg daily. Furthermore, in children with DYT1 dystonia, baclofen improved leg dystonia and gait in 14 out of 33 patients with a dosage above 50 mg daily and nine patients reported prolonged and stable benefit [63]. Patients with milder dystonia at the start of therapy tended to have a better clinical response. However, the response to baclofen in adults with focal dystonia was less impressive, ranging from minimal improvement to no benefit [42,66]. Side effects of baclofen include lethargy, drowsiness, dizziness, dry mouth and urinary urgency or retention, which can prevent treatment with the high doses of baclofen necessary to improve dystonic symptoms. A rapid decrease or abrupt discontinuation of baclofen may precipitate psychosis or seizures so that slow tapering of baclofen is recommended.

Baclofen is absorbed into the bloodstream rapidly. However, because of the blood–brain barrier, corresponding cerebrospinal fluid (CSF) level are usually significantly lower than expected [67]. This observation may, in part, explain the limited efficacy of oral baclofen therapy. Narayan and colleagues found that intrathecal baclofen (ITB) was effective for treatment of dystonia in an 18-year-old man with severe cervical and truncal dystonia refractory to all oral therapy and to large doses of paraspinal botulinum toxin injections [68]. Within a few hours of ITB infusion, his dystonia improved markedly. Subsequent studies confirmed the benefits of ITB in different forms of dystonia and spasticity, including segmental or generalized dystonia, dystonic cerebral palsy, stroke, head injury, tardive dystonia, Friedrich’s ataxia, pantothenate kinase-associated neurodegeneration, parkinsonism and reflex sympathetic dystrophy, but not conclusively in primary generalized dystonia [69–78]. Significant benefits were demonstrated as a reduction in muscle tone and spasticity and improved quality of life, activities of daily living, level of function and cost effectiveness [79–81]. However, it is presently unclear whether ITB can induce lasting improvement in patients with dystonia. Ford and colleagues failed to demonstrate a significant predictable or consistent difference in dystonia and disability score following ITB [82]. However, these results may have been owing to the small sample size, failure to optimize the dose of baclofen or insensitivity of the rating scale which was used [14].

In the past, the usual indication for ITB in some centers has been severe, generalized dystonia refractory to oral medications, although, currently, stereotactic globus pallidus DBS is increasingly considered in this setting. ITB has also been shown to be effective in patients with hemidystonia or segmental dystonia [72,78]. More specific indications include increased comfort, enhanced function and greater ease of positioning or care. ITB is particularly helpful for patients with dystonia when accompanied by spasticity, such as in stroke, head injury or cerebral palsy [70,78,83]. Patient reliability and compliance are also critical for the success of ITB therapy since they must return for periodic pump refills and dose adjustments. Despite limited and preliminary results, the American Academy for Cerebral Palsy and Developmental Medicine published a systematic review of the use of ITB for spastic and dystonic cerebral palsy, supporting the benefit of ITB in reducing spasticity and dystonia, particularly in the lower extremities [84].

ITB is administered via an implanted pump connected to an intrathecal catheter (FIGURE 1). Before a pump is implanted for long-term therapy, responsiveness to ITB should be tested in one of two ways: by bolus injection or continuous infusion. The purpose of screening is to identify patients whose dystonia is likely to respond to ITB infusion. Although there is no accepted standard regarding a clinically significant response to an ITB trial in dystonia, most specialists accept a significant (for example 25%) reduction in the Barry–Albright Dystonia (BAD) or BFM scores during two consecutive time intervals [14]. After implantation for dystonia, improvement typically occurs in 2–3 days, which is the time required for the medication to reach the cerebral convexities, compared with 2–4 h in spasticity. After intrathecal infusion, the concentration of baclofen within the cervical region and brain has been shown to be less than that within the lumbar region [85]. The mean baclofen dose at the time of response was 485 µg/day [72]. Dystonia also requires higher doses than spasticity as more...
medication is probably needed to achieve therapeutic concentrations at a cortical level [86]. Approximately 10% of patients with severe generalized dystonia lose their responsiveness to ITB over time. This may occur as early as during the first year of therapy. Whether the lack of response is due to development of tolerance or progression of symptoms is uncertain. Other side effects, which may occur in approximately 25% of patients, include constipation, infection, CSF leaks, respiratory depression or catheter malfunction. Lastly, worsening dystonia has been reported after ITB, which is speculated to be a result of a reduction in spasticity [87].

**Antidopaminergic drugs**

There appear to be a group of patients with dystonia who respond favorably to dopaminergic agents and others who improve with the oppositely acting dopamine antagonist drugs (dopamine receptor blocking agents [DRBAs] and dopamine depletors). The effect of DRBAs is paradoxical as they cause both acute and tardive dystonia in some patients [88]. While positive effects have been observed in several case reports and case series with DRBAs, most clinical trials have produced mixed results [42,43]. In addition, undesirable side effects are common, including sedation, parkinsonism and tardive dyskinesia. Therefore, the use of DRBAs, particularly traditional typical neuroleptics, for the treatment of dystonia is discouraged. However, notable exceptions have been reported with clozapine and risperidone (both atypical neuroleptics) in a small number of open trials. Clozapine has been reported to be moderately effective in the treatment of segmental, axial and generalized dystonia but with conflicting results in patients with spasmodic torticollis [89–92]. Clozapine should be initiated at a low dose of 12.5 mg/day with slow increments of 12.5–25 mg/week until clinical improvement or side effects are observed. While subjective improvement has been reported in patients with cervical dystonia with a dose ranging between 37 and 100 mg/day, much higher doses (450–900 mg/day) have been required in patients with axial, truncal or generalized dystonia [89,91]. Although these results are promising, its efficacy has not been verified in a controlled trial. A further advantage of clozapine is that it does not cause tardive dyskinesia and rarely causes acute extrapyramidal side effects associated with conventional neuroleptics. Clozapine has, in fact, been used to treat tardive dyskinesia in some patients and may be effective in tardive dystonia [93–95]. Any use of clozapine needs to be closely monitored for agranulocytosis and the dose should be maintained at the lowest effective dose to minimize side effects. Risperidone (a D₂ receptor blocking agent with a high affinity for 5-hydroxytryptamine [HT₁₂] receptors), at a dose between 1.5 and 3 mg/day, has been demonstrated in one trial to decrease duration and amplitude of involuntary movements in segmental and generalized dystonia [96]. However, the risk of developing tardive syndromes is generally considered to be higher for risperidone, compared with clozapine.

Tetrahydrozine (TBZ) has an advantage over conventional neuroleptics in that it rarely causes dystonic reactions and to date there have been no documented cases of tardive dyskinesia secondary to TBZ. [97]. It acts as a reversible high-affinity inhibitor of monoamine uptake into granular vesicles of presynaptic neurons and a secondary depleter at low doses, as well as a weak D₂ postsynaptic receptor blocker at high doses [98]. TBZ has been shown to be effective in various forms of generalized and focal dystonia in small double-blind crossover studies, large open studies and retrospective data analysis [97,99–101]. Furthermore, TBZ has been proven to be moderately effective in a large variety of hyperkinetic movement disorders, particularly in chorea and focal dystonia/dyskinesias [97,99,100]. The effects of TBZ can be further modulated by lithium, either by augmenting the therapeutic efficacy of TBZ or by allowing a reduction in the daily dose of TBZ in patients who have already experienced side effects [100,102,103]. Moreover, in some patients, TBZ has been combined with levodopa to ameliorate side effects of parkinsonism [104]. Among various forms of dystonia, TBZ resulted in a marked improvement in 80.5% of patients with tardive dystonia and 62.9% of idiopathic dystonia, including oromandibular dystonia (OMD) [97,105]. The average maximum dose of TBZ was approximately 100 mg daily, ranging from 12.5 to 400 mg. Long-term benefits have been reported for up to 180 months (average 28.9 months) [97]. Common side effects of TBZ include drowsiness, parkinsonism, insomnia, depression, nervousness, anxiety and akathisia, which improve with reduction in dosage [97]. The treatment of TBZ-induced depression remains to be investigated. Overall, TBZ is considered to be an effective and safe drug for the treatment of dystonia. Unfortunately, it is not currently available in the USA, but can be obtained from the UK or Canada under the trade names Nitoman® or Xenazine 25®.

**Other pharmacological agents**

Many patients with dystonia require a combination of several medications for effective treatment. In fact, Marsden and colleagues proposed a triple therapy, consisting of a dopamine depletor (reserpine or TBZ), a dopamine receptor blocker (pimozide) and an anticholinergic drug (benzhexol) for treatment of severe dystonia [56]. In addition to the medications already discussed, there are scattered, largely open-label reports concerning the efficacy of a variety of other miscellaneous drugs in the treatment of dystonia. In an open study, Greene and colleagues reported that clonazepam and other benzodiazepines were effective in 15% of 177 patients with idiopathic dystonia [42]. Since then, a number of open and retrospective studies have followed, which demonstrated improvement of blepharospasm, dystonic choreoathetosis, cervical dystonia and secondary dystonia with benzodiazepines, particularly clonazepam [20,106]. Clonazepam may be particularly effective in myoclonus dystonia [42,107]. Dosages of clonazepam range from 1 to 4 mg daily and dose increases may be limited by sedation. Currently, there is no evidence for superiority of any particular benzodiazepine. Tizanidine is a centrally acting muscle relaxant that works through agonistic activity at noradrenergic α-2 receptors [108]. Tizanidine has primarily been used to control spasticity in pyramidal disorders and its efficacy in the treatment of dystonia has not been extensively studied [109]. Since, in practice, tizanidine...
is commonly used to treat dystonia with uncertain results, a controlled trial is needed to determine its efficacy [110]. Mexiletine, an anti-arrhythmic drug related to lidocaine, has been demonstrated in small case series to improve blepharospasm and cervical dystonia for 3–6 months [111–113]. Alcohol has been reported to be effective in some patients with autosomal dominant dystonia with lightning jerks, currently known as M-D [114]. Riluzole has reportedly been helpful in a small number of patients with spasmodic torticollis refractory to other therapies [115].

**Botulinum toxin therapy**

BTX treatment has become a standard therapy for focal dystonia. BTX does not affect the synthesis or storage of acetylcholine (Ach), but inhibits Ach release at the neuromuscular junction [116,117]. Following local injection into muscles, the toxin enters the nerve terminal via endocytosis, interacts with intracellular proteins and inhibits the vesicular release of Ach at the neuromuscular junction [116,118]. Inhibition of Ach produces chemical denervation and partially weakens striated muscle. Paralysis usually peaks 3 weeks after the injection. Because of molecular turnover within the neuromuscular junction and neuronal sprouting, muscular activity begins to return at 3 months, with restoration of complete function at approximately 6 months [119]. BTX-A is one of seven botulinum neurotoxin serotypes known alphabetically as types A through G [120,121]. Although these toxins have different intracellular targets, their biological activity at the neuromuscular junction is similar [122]. While the light chain of BTX-A and E cleaves synaptosome-associated protein (SNAP-25), a protein needed for synaptic vesicle targeting and fusion with the presynaptic membrane, the light chains of BTX-B, D and F prevent the quantal release of Ach by proteolytically cleaving synaptobrevin-2, also known as vesicular-associated membrane protein (VAMP) [116,123]. Of these serotypes, only A and B are currently available as commercial preparations. Types C and F have also been used in humans, but only on an experimental basis. The first commercial preparation of botulinum neurotoxin to be used clinically was based on the A serotype (Botox®) and this product continues to be used in many countries throughout the world. Another preparation based on the A serotype (Dysport®) was later introduced in several countries and may become available in the USA within several years. In the year 2000, a product based on the B serotype (Myobloc®/Neurobloc®) became commercially available. Although all of these formulations inhibit Ach release, both BTX-A formulations do so at the same sites, while BTX-B formulations act at different sites [119,124].

Currently, the US FDA approves BTX-A as a therapeutic agent for patients with strabismus, blepharospasm, cervical dystonia and other facial nerve disorders, including hemifacial spasm. The US FDA approved BTX-B (Myobloc) as treatment for cervical dystonia. BTX is considered the treatment of choice for blepharospasm, OMD and laryngeal dystonias. Many patients with cervical and limb dystonias also benefit from botulinum toxin alone or in combination with oral medications. Response rates vary according to the form of focal dystonia, but range from 70 to 90% improvement. In addition, numerous studies have confirmed the safety of BTX injections in focal dystonias [125,126]. Despite limited US FDA approval for some of the above indications, the use of BTX is rapidly expanding to include a variety of neurological, gastrointestinal and dermatological disorders [127,128].

A small percentage of patients receiving repeated BTX injections develop antibodies against BTX, causing them to be completely resistant to the effects of subsequent injections [129,130]. The frequency of immunoresistant patients in treated dystonic populations has been reported to vary from 3.1 to 4.3%, while the Allergan package insert indicates the prevalence of antibody with the 79–11 lot to be 17% in a population with torticollis [129,131]. The Mouse Protection Assay (MPA) is considered a gold standard method of detecting BTX antibodies [132]. Although the factors that predispose to the development of antibodies have not been precisely identified, large doses of BTX (> 250 U of BTX-A), large cumulative doses, young age and injections administered at less than 3 month intervals (booster injections) are probable risk factors for the development of resistance [129,131–133]. As a result, physicians are warned against using booster injections, encouraged to extend the interval between treatment as long as possible and advised to use the smallest effective dose. BTX resistance primarily affects cervical dystonia (CD) patients and is only rarely observed in patients with blepharospasm, presumably because of the larger doses used to treat CD [134]. Some patients with BTX-A antibodies have benefited from injections by immunologically distinct preparations, such as BTX-B and BTX-F [135,136]. After 1–3 years without BTX exposure, resistant patients may become antibody negative but typically experience only transient benefit from BTX owing to reappearance of antibodies [137].

Considerable variation exists among physicians regarding injection techniques, the number of injections used per muscle, doses per muscle, combinations of muscles injected and the use of electromyogram (EMG) guidance in various forms of dystonia [138,139]. The details of this are beyond the scope of this review.

**Botulinum toxin therapy in CD**

CD is the most common form of adult-onset focal dystonia. It manifests as involuntary neck muscle contractions that cause twisting or turning of the neck and shoulder in a number of directions (FIGURE 2) [140]. In most CD patients, pharmacological therapy is ineffective, only partially effective, or complicated by unwanted side effects [141]. This is in contrast to 70–90% response rates in CD patients who experience benefits from BTX injections, demonstrating improvement in function and control of the head and neck, reduction in pain and improved quality of life. As a result, BTX injections are now considered as first-line therapy for the treatment of CD. Benefits may also extend to the prevention of secondary complications, such as cervical radiculopathy, myelopathy, contractures and improvement of symptoms of depression [142–144]. Using TWSTRS and other scales, the efficacy and safety of BTX (both BTX-A and BTX-B) has been demonstrated in several controlled and open trials [145–156]. In general,
open label studies have tended to report more dramatic improvement, probably because of greater flexibility in the placebo effect and a greater flexibility in selecting appropriate doses and sites of injection in individual patients. Although most studies utilized BTX-A, more recent studies using BTX-B have demonstrated its efficacy in both BTX-A responders and BTX-A-resistant patients [150,154–157]. In one comparative study between single doses of BTX-A (Botox® 250 U) and BTX-B (Myobloc®)
10,000 U), both serotypes had equivalent benefit in CD patients at 4 weeks, but BTX-A had fewer adverse events and a marginally longer duration of effect in patients showing a clinical response [158]. A slightly shorter duration following BTX-B may be in part owing to incomplete muscle paralysis produced by this agent following injections [159,160]. One study was conducted retrospectively using BTX-F in 18 BTX-A resistant patients [161]. Although all patients initially improved, four patients became rapidly resistant to BTX-F. A comparison of BTX-A (Botox®, 292 U in the first session and 262 U in the second session) with trihexyphenidyl (16.2 mg) in a prospective randomized, double-blind design, showed significant improvement by the TWSTRS scale in favor of BTX-A, and adverse effects were less frequent than in patients assigned to trihexyphenidyl [162,163]. Furthermore, a number of long-term studies confirmed that most patients derive long-term benefits as well as satisfaction and approximately 75% of patients continued to benefit for at least five years, 7.5% developed secondary failures and only 1.3% discontinued treatment because of intolerable side effects [134,164,165].

The average latency between injection and the onset of improvement is 1 week (range 1–8 weeks) and peak effect begins approximately 16 days following injection. The average duration of benefit is 11–14 weeks. However, additional benefit may continue for another 6 weeks in some patients. On average, injections need to be repeated every 3–4 months. Patients with simple CD, such as rotation or tilt, and with shorter duration of symptoms usually respond better, but the most important factor for a favorable response is the proper selection of the involved muscles and dosage. Different EMG patterns have been described with various neck postures for BTX treatment planning [166]. The average optimal total dose per visit, in CD patients is approximately 200 U of Botox®, 500 U of Dysport® and 10,000 U of Myobloc™ [167]. Most studies recommend a 3:1 Dysport®/Botox® equivalency ratio [168–170].

BTX injection in CD is rarely associated with significant complications. However, most studies report side effects in 20–30% of patients per treatment cycle and approximately 50% of patients experience these at some time during therapy. Side effects are always transient and usually resolve within several days. Dysphagia is the most common side effect after cervical injections and is probably related to regional spread of the toxin into the pharyngeal muscles [171]. Women with thin necks are more likely than men to develop dysphagia, particularly if both sternocleidomastoid muscles are injected [148]. Other common side effects include neck weakness and local pain. BTX-B appears to cause more transient local pain at the time of injection, probably as a result of its acidic pH. BTX-B is also associated with a higher frequency of dry mouth [150,156]. Many cases of later response failure occur as a result of poor injection technique or progressive changes in the severity of dystonia and/or the pattern of involved muscles. Therefore, it is important to reassess the patient’s dystonia clinically or by EMG mapping in order to modify BTX doses and muscle distribution appropriately. Truly resistant patients usually benefit from injections with other serotypes of BTX [150,155,172]. Current preparations of BTX-A, with a lesser protein load of 5 ng of protein/100 U, are associated with a lower risk of antibody formation, compared with original BTX-A preparations [173].

**BTX therapy in blepharospasm & OMD**

Blepharospasm is a form of focal dystonia that results in bilateral involuntary forceful contraction of the orbicularis oculi [174]. Next to CD, it is the most common form of focal dystonia [175]. This contraction results in increased blink rate, forceful eye closure and difficulty opening the eyes; in severe cases, it may cause functional blindness. Similar to CD, pharmacological therapy is often associated with more side effects than effectiveness. Therefore, BTX-A injection is generally accepted as the treatment of choice for blepharospasm with success rates of approximately 90% [126,153,176–187]. Although there are many studies demonstrating efficacy of botulinum toxin in blepharospasm, most of them are small. Two controlled trials compared Botox and Dysport, but without a placebo group [188,189]. Despite the lack of high-quality controlled trials, a review of available data from 55 open case-controlled studies with a total of more than 2500 patients and data compiled by the American Society of Ophthalmology demonstrated a success rate of approximately 90% [190]. Several studies also report improved quality of life after treatment with botulinum toxin [191,192]. In addition to essential blepharospasm, the efficacy of BTX-A injections has been demonstrated in patients with blepharospasm from drugs, parkinsonism (particularly progressive supranuclear palsy) and in patients with associated apraxia of eyelid opening [193,194]. Furthermore, effectiveness of BTX-A treatment may be partly influenced by the position of the injection sites around the orbicularis [195]. BTX-A should be injected into the pretarsal rather than the preseptal portion of the orbicularis oculi for effective treatment of blepharospasm and is especially essential for treatment of lid opening apraxia [196]. In addition to orbicularis oculi, other muscles, including the corrugator supercilii, the frontalis and the procerus, may be involved in blepharospasm and require injection. BTX begins to work 1–10 days after injection and reaches peak effect within 2–4 weeks. The typical duration of action is 3–4 months but this varies considerably. EMG is seldom used to guide injections into the upper facial muscles since the injections are administered subcutaneously rather than intramuscularly. Long-term follow-up of patients receiving multiple treatments demonstrated sustained improvement, with reduction in spasm intensity [180,197]. Unlike CD, the likelihood of resistance development to BTX despite a long period of treatment, is very low. On the other hand, side effects from BTX-A injection in the periorcular muscles are relatively common, particularly early in therapy before dose optimization, although they are generally mild and transient. Ptosis is the most frequent adverse effect (10–20%) and can be prevented by avoiding injections into or spread to the midline levator palpebrae muscle [181,198,199]. The risk of ptosis is four-times greater in patients who have had previous blepharoplasty than in unoperated patients [200]. Other side effects include dry eyes, tearing, periorcular ecchymosis, corneal ulcerations and rarely diplopia related to spread into an extraocular muscle.
OMD is a form of focal dystonia that involves masticatory, lower facial, labial and lingual musculature. The term CD is used for any dystonia that occurs above the neck. A variant of OMD, Meige’s syndrome refers to a combination of OMD and blepharospasm [201]. The involvement of masticatory muscles in OMD may cause jaw-closing, jaw-opening, lateral deviation, protrusion, retraction or a combination of these movements. These movements often result in involuntary biting of the tongue, cheek or lips and difficulty with speaking and chewing. Its appearance is often disfiguring and socially embarrassing [202]. By far the most common presenting type of spasm begins in the upper facial muscles with lower facial muscles becoming involved later which causes lip-pursing, grimacing and resultant difficulty in articulation [201]. Some patients with OMD may present with weight loss, which can be a medical emergency. In most patients with OMD idiopathic and tardive dystonia is the most common cause of secondary OMD [203,204].

BTX has become the therapy of choice for OMD and its use in jaw-opening, jaw-closing and jaw-deviation OMD is documented [153,205–207]. Most of the treatment studies in OMD have been open-label trials, but all have reported improvement [126,205,206,208–213]. However, jaw-opening dystonia is more difficult to treat with less consistent results than jaw-closing dystonia [205].

**Botulinum toxin therapy in laryngeal dystonia**

Laryngeal or spasmodic dysphonia (SD) is a focal dystonia resulting in a strained, strangled or hoarse voice. There are three types of spasmodic dysphonia: the adductor type, the abductor type and the mixed type. Adductor spasmodic dysphonia (ADSD) is by far the most common (approximately 90%) and is characterized by a strained-strangled voice with intermittent voice breaks due to overadduction of the vocal folds, resulting in a staccato-like effect [214,215]. Abductor spasmodic dysphonia (ABSD) is less common (approximately 10%) and is characterized by intermittent breathy breaks, associated with prolonged abduction folds causing voiceless consonants in speech [214–216]. In the mixed type, the patient has features of both. Speech studies have demonstrated that SD is a movement-control disorder affecting vocal-folds during phonation onset with no laryngeal movement difficulty [217].

In the past, surgery was the only available treatment option for patients with spasmodic dysphonia until Blitzer and colleagues performed the first BTX treatment on a SD patient [218]. Prior to its use in SD, BTX injections had been used successfully to treat other focal dystonias, such as blepharospasm [187,219,220]. Previous success at their institution with blepharospasm led to the use of BTX in SD, subsequently confirmed by numerous prospective and one double-blind study [221–227]. A meta-analysis of 30 studies, most of which were single-blinded, indicated moderate overall improvement as a result of BTX treatment [228]. The Cochrane Collaboration reviewed the use of BTX for SD reporting positive effects related to length of treatment effect, degree of improvement, patient satisfaction and observed side effects [229]. The standard treatment for ADSD is a bilateral thyroarytenoid injection of equal amounts of BTX-A, while ABSD is treated with bilateral posterior cricoarytenoid or sometimes cricothyroid injections. On average, patients treated for ADSD with BTX-A experience a 97% improvement in voice [230]. All studies have reported similar results, patient satisfaction and side effects with a duration of benefit of approximately 15.1 weeks [202,231–234]. Based on this evidence, the American Academy of Otolaryngology-Head and Neck Surgery endorses BTX-A as primary therapy for SD (Policy statement: Botulinum toxin. Reaffirmed March, 1999).

Following BTX-A injections, there may be an initial period of marked muscle weakness lasting for several days, which later improves to a milder weakening that constitutes the principal therapeutic effect. In ADSD, this is the cause of the breathy dysphonia that immediately follows thyroarytenoid injections in approximately 35% of patients [222,235]. Other side effects include mild feelings of subjective choking in 15% of patients and frank dysphagia in a much smaller number of patients [222,235]. Applications of BTX in the larynx have expanded to include spasmodic laryngeal dyspnea, stuttering, voice tremors and criocopharyngeal muscle spasm.

**BTX for limb & occupational dystonia**

Like other dystonias, limb dystonia refers to excessive muscle contraction resulting in abnormal postures. When affecting the hands, the abnormal movements can be task-specific, thus interfering with the patient’s daily activity and occupation. Focal hand dystonia is often named by the specific function that is impaired and typically presents as task-specific muscle spasms. Therefore, this form of dystonia has also been called writer’s cramp, occupational cramp or musician’s cramp [236]. Simple writer’s cramp, the most frequent form of idiopathic limb dystonia, refers to difficulty limited only to the act of writing and with no other manual task (FIGURE 3). As soon as patients pick up a pen or within a word or two, dystonic postures of the hand appear, which impede the speed and accuracy of writing and during no other manual task. A wide variety of abnormal postures may occur. There may be excessive gripping of the pen, excessive finger or wrist flexion, ulnar deviation of the wrist and occasionally elevation of the elbow and shoulder [237]. In other forms of arm dystonia, dystonia can also occur while carrying out other manual tasks, such as when using tools or eating utensils, applying make-up or shaving.

In addition to writer’s cramp, other activities can be affected by focal dystonia. Examples include tailor’s dystonia, shoemaker’s dystonia, telegraphist’s dystonia and auctioneer’s dystonia. Musicians are especially prone to develop these disorders, possibly related to their demanding training regimens and prolonged practice schedules [238,239]. They have occurred in musicians using almost any kind of instrument but are more common in piano players (FIGURE 4). Embouchure dystonia refers to a form of focal task-specific dystonia of the lips, jaw and tongue muscles while playing a brass or woodwind instrument [240].

Although BTX has not yet been approved in the USA for use in limb dystonia, numerous open-label studies of BTX treatment of focal hand dystonia have demonstrated good results [241–245]. More than 70% of subjects reported a similar degree of subjective
The most common adverse effect of BTX treatment for limb dystonia is muscle weakness, which invariably appears to some extent in all injected muscles. Diffusion of BTX away from the injection site into un.injected muscles may cause unexpected loss of strength in the involved region and impair the patient’s ability to perform tasks previously unaffected by dystonia. For example, excessive weakness often occurs in third finger extensors after wrist extensors are injected, impairing fine motor task in the select group of patients who require the highest degree of motor control, such as dentists and musicians [249]. Fortunately, any excessive weakness that occurs is usually short lived, lasting only several weeks.

Surgical treatment of dystonia

The surgical treatment of dystonia has been performed for decades, largely owing to the lack of other effective treatment options. Previous procedures include ablative thalamic surgery and peripheral denervation procedures [250,251]. However, reported results were highly variable, with 50% of patients demonstrating variable degrees of partial improvement [252]. Recently, there has been a resurgence of interest in the surgical treatment of dystonia because of dissatisfaction for medical therapy for generalized dystonia, greater understanding of the pathophysiology of dystonia and improving technology, especially advanced neuroimaging and neurophysiological recording resulting in more precise localization in the basal ganglia.

DBS & central ablative procedures in dystonia

Although there are no data from normal humans, microelectrode recordings from patients with generalized dystonia indicate that the mean discharge rates (∼50 Hz) in the globus pallidus interna (GPi) are lower than those in patients with PD (∼80–85 Hz), parkinsonian primates (∼70–75 Hz) and even less than in normal nonhuman primates [253,254]. Importantly, the firing pattern is irregular and grouped, with different spatiotemporal patterns [255–257]. Based on earlier models of hyperkinetic movement disorders, one could not have predicted that GPi lesions (pallidotomy) would improve dystonia; in fact, one would predict that GPi lesions should make dystonia worse [258]. Instead, there are many reports of efficacy of pallidotomy or pallidal DBS in patients with generalized dystonia [17,254,259–264]. Exactly why this procedure works is not known, but it is unlikely that alterations in firing rates alone can explain the benefits after pallidotomy. It has been suggested that the abnormal pattern of neuronal discharge in GPi, rather than discharge frequency, which is pathophysiologically relevant to dystonia, explains the observed
improvement following pallidotomy or GPi DBS \([254,265]\). Disrupting abnormal GPi activity results in a decrease in cortical overactivation; thus, improving dystonia.

Therefore, GPi has become the most common target in dystonia surgery, particularly in the posteroverventrolateral region and is the same location used for pallidal surgery in PD \([266]\). However, it is slightly anterior to the usual pallidotomy target, in order to avoid the spread of current to the internal capsule with the higher intensity of stimulation usually required for treatment of dystonia. GPi DBS has largely replaced pallidotomy because of lower postoperative morbidity compared with standard radiofrequency lesioning and the ability to control stimulation-induced side effects by adjusting stimulator settings. In view of the bilateral involvement of basal ganglia circuitry in generalized and segmental dystonia, most patients with dystonia are considered for bilateral stimulation and the two electrodes are usually implanted in the same surgical session (FIGURE 5) \([266]\). Unilateral approaches should be reserved for patients with hemidystonia or focal dystonia \([267]\). The postoperative improvement of dystonia after GPi DBS may be delayed, taking up to several months in some cases, before full benefit is achieved, which contrasts with the more rapid improvement that occurs in PD or tremor \([268]\). There is clearly a gradual, but progressive and sustained improvement with GPi stimulation, with early response of phasic dystonic movements followed by the improvement of tonic movements \([264]\). The settings are usually adjusted frequently during the first year after surgery with only minimal adjustment required later \([269]\). The energy consumption is much higher in dystonia than in PD, which is attributed to the broader pulse width and voltages required for symptomatic improvement. Depletion of the batteries may therefore occur within 2 years. (By contrast, dystonia usually recurs within minutes when the pulse generators are switched off \([269,270]\)).

Patient selection is extremely important in order to ensure a successful outcome from movement disorder surgery. A multidisciplinary team including a neurologist, neurosurgeon, neuropsychologist and nurse practitioner is often necessary to comprehensively evaluate a patient’s suitability for surgery. In general, surgery should be considered in patients with generalized dystonia, as these patients are the most severely affected and most refractory to therapy \([269,270]\). Recently, refractory cases of CD have undergone bilateral GPi DBS with good results but with relatively short-term follow-up \([271–273]\). Surgery has been a lifesaving procedure in some patients with status dystonicus \([274,275]\). In addition, patients being considered for surgery must have responded unsatisfactorily to conventional and less invasive treatment. These include pharmacological agents and BTX, which have already been discussed. Lastly, the timing of surgery should be assessed with respect to when the advantages of surgery outweigh surgery and the risks of medical treatment. Patient quality of life based on personal, professional and social factors is an important factor that physicians must use to assess the risk:benefit ratio of surgery.

Figure 4. Piano playing dystonia, a form of task-specific dystonia.

Figure 5. Magnetic resonance imaging brain scan in a patient with generalized dystonia and bilateral electrodes in both globus pallidus interna.
The efficacy of both pallidotomy and pallidal DBS in dystonia have been similar and encouraging. The best improvement was achieved in patients with DYT1-positive dystonia, with a mean improvement ranging from 48 to 90% in the BFM dystonia scores at a follow-up of at least 1 year [17,259,263,264,266,273,276–284]. However, a more recent study indicated that remarkable improvement can also be achieved in non-DYT1 patients [264]. Drugs were reduced in many patients, resulting in improvement of alertness and school performance. The effect of DBS has also had a favorable impact on quality of life in patients with dystonia [285,286]. Adverse neurological effects have been infrequent but DBS-related hardware complications may occur [270,287]. Preliminary results have found no deterioration in cognitive scores and neuropsychiatric measures following GPi DBS [285]. On the other hand, pallidal surgery in patients with secondary dystonia appears to be much more complex than that for primary dystonia. Patients with secondary dystonia respond less well (mean improvement of 29% in BFM scores at 1-year follow-up) and poorer results have occurred in patients with secondary dystonia owing to structural lesions [283]. Nevertheless, some patients with secondary dystonias, for example, panthothenate kinase-associated neurodegeneration, post-traumatic dystonia, dystonic cerebral palsy and tardive dystonia, have experienced meaningful benefit [274,275,288–292]. However, published experience has typically been limited to case studies or small retrospective case series. Recently, bilateral GPi DBS has also been shown to be beneficial in patients with segmental dystonia, Meige’s syndrome, blepharospasm, myoclonus dystonia and cervical dystonia [262,273,293–296]. GPi DBS remains a relatively safe procedure in experienced hands, with less than 2% permanent severe morbidity and a low rate of (3–4%) of infection or damage to the implanted materials. After a review of 34 studies in which 201 people with primary or secondary dystonia had the device implanted and received DBS, the US FDA has approved the use of GPi DBS in patients with primary dystonia.

Peripheral surgery in dystonia
Prior to the introduction of BTX, peripheral surgery was used in some patients with focal dystonia, particularly in CD. Although no head-to-head comparison is available between BTX treatment and peripheral surgery, the place of surgical treatment has been limited and reserved for those patients who fail BTX treatment and experience functional disability. Three procedures have been performed in the treatment of CD: extradural selective sectioning of dorsal rami or posterior ramisectomy, anterior cervical rhizotomy, and microvascular decompression of the spinal accessory nerve [297–299]. Rhizotomies and ramisectomies improve CD by selectively denervating and weakening the overactive musculature. Among these three procedures, posterior ramisectomy is considered to be the procedure of choice, although no study has formally compared the different surgical approaches [250]. Posterior ramisectomy is less invasive than the intradural procedure and appears to produce similar or better postoperative benefit with lower complication rates. Rhizotomy has been shown to markedly improve 85% of patients with CD in retrospective studies [299,300]. Only approximately 40% of patients achieve an excellent long-term outcome of up to 6.5 years following rhizotomy, ramisectomy or myotomy [293]. Based on this evidence, peripheral surgery for CD may remain a viable alternative in the management of CD, but should be carefully tailored to the individual patient.

Physical, supportive & future therapies
In addition to the above treatment options, it is important to emphasize the role of patient education, physical rehabilitation and supportive care as these are important components of a comprehensive approach to the patient with dystonia. Since sensory dysfunction has been demonstrated in patients with focal hand dystonia, the use of sensory training has been proposed to treat the disorder [301–304]. Byl and McKenzie reported improvement in patients with focal hand dystonia after multimodal retraining designed to excite cortical areas associated with area 3b (somatosensory) and 3a ( proprioception, vibration and muscle afferents) [305]. Zeuner and colleagues used training in Braille reading as a method of sensory training to demonstrate improvement in spatial discrimination with decreased disability in patients with focal hand dystonia [306–308]. In addition to sensory training, various devices or methods, such as hand orthosis, splint immobilization, sensory feedback therapy and transcranial magnetic stimulation, have been used to treat focal dystonia [309–314]. Despite the occasional occurrence of immobilization-induced dystonia [314], hand and forearm immobilization for 4–5 weeks has been reported to improve symptoms for up to 12 months in eight patients with idiopathic occupational dystonia [315,316]. Prolonged immobilization may normalize the abnormally enlarged cortical representation of dystonic muscles by a detraining process (inactivity-dependent neuroplasticity). A potential use of muscle afferent block by intramuscular blocking with lidocaine and alcohol has been suggested for treatment of drug-resistant OMD [317]. Inhibiting expression of mutant TorsinA may be a potential future strategy for the treatment of DYT1 dystonia [318]. Although not evaluated for its safety and efficacy, dystonia patients increasingly utilize complementary and alternative medicine methods, in addition to conventional treatments [319]. While promising, the efficacy of these new approaches remains to be confirmed in prospective clinical trials.

Lastly, general physical therapy can be a helpful adjunct to treatment plans. Gait training, muscle strengthening and stretching are modalities used in patients with dystonia to improve general well-being and to prevent falls and contrac- tures. Various assistive devices may allow patients to regain some independence and to perform tasks that are otherwise difficult or impossible. Patient support groups offer a forum for patients and caregivers to receive education and share experiences about symptoms, diagnosis and treatment options.

Conclusion
The field of dystonia treatment is expanding, particularly with the advent of new pharmacological agents, different forms of BTX and GPi DBS. Although specific treatment is available in only selected dystonic syndromes, such as Wilson’s disease and
DRD, for the great majority of dystonic patients treatment is aimed at controlling symptoms rather than treating its cause. For patients with childhood-onset dystonia, most of whom later develop generalized dystonia, oral medication is the mainstay of therapy (FIGURE 6). Among pharmacological agents, anticholinergic drugs are the most useful and effective, with approximately 50% of children responding at least moderately. For those with adult-onset primary dystonia in which the dystonia usually remains focal, BTX is usually the treatment of choice. In patients who are refractory to such treatments, GPi DBS should be considered, particularly in patients with primary generalized dystonia. With recent advances in molecular biology which have led to a better understanding of underlying pathophysiology, the possibility of suppressing expression of mutant TorsinA is a potentially new strategy in the treatment of DYT1 dystonia and possibly other forms of genetically determined dystonia [318].

Expert commentary
Dystonia is a syndrome, not a disease, comprised of abnormal dynamic movements of different etiologies. The initial evaluation of the patient with dystonia aims at establishing the diagnosis and classifying the dystonia according to the age at onset, distribution and etiology. Generally, a specific cause may be identified in 40% of patients with childhood-onset dystonia, which occasionally results in specific treatment, such as in Wilson’s disease, DRD, and biotin deficiency. In most cases of dystonia, treatment is symptomatic and designed to improve posture, function and relieve associated pain. Therefore, therapeutic choices are generally guided by clinical assessment of the topography of dystonia, severity of abnormal movements, functional impairment and progression of disease. Because of the response to levodopa in DRD, all patients with childhood onset generalized segmental dystonia and occasional appropriately selected adults with dystonia should be considered for a therapeutic trial of levodopa. Response almost always occurs at a dose of 300 mg/day, when combined with a dopa decarboxylase inhibitor. If successful, therapy should be maintained at the lowest effective dose. If ineffective, anticholinergics should be tried next, as this class of drug has been found to be the most helpful, especially in children. Since side effects of anticholinergics usually limit its use (in adults more than children), the dose should be slowly titrated to the maximum tolerated dose. If anticholinergics are not helpful or only partially effective, baclofen should be considered as an adjunctive therapy. Dramatic improvement may occur in children, particularly those with limb dystonias. Other drugs are tried later, usually in combination or occasionally alone, such as benzodiazepines or DRBAs. TBZ, a presynaptic dopamine depletor, has been reported to be beneficial, not only in dystonia, but also in various hyperkinetic movement disorders and may be considered where this drug is available. As a general guide, when initiating an oral medication, the key is to start at a low dose, slowly titrate to minimize side effects and to use the lowest effective dose. All drugs should be given in divided doses throughout the day. It is also important to reassure patients of a possible delayed response and that they need to be patient while awaiting this. When the above therapies fail, intrathecal baclofen or surgery may be considered. Although various surgical procedures are available, GPi DBS has recently gained popularity owing to its excellent results, safety, programming adjustability and reversibility. In general, patients with primary dystonia respond well while patients with secondary dystonia respond less well and poorer results are obtained in patients with structural lesions. Occasionally, some patients with primary dystonia may exhibit acute life-threatening dystonic symptoms, so-called dystonic storm or status dystonicus, with rhabdomyolysis, respiratory failure and renal failure, requiring urgent management in an intensive care unit [13].

BTX injections have become a mainstay of therapy for focal and segmental dystonia, including tardive dystonia. Its therapeutic effect results from weakness of the injected muscles, with resultant improvement of the focal dystonic symptoms lasting up to 3–6 months. BTX treatment is very effective as demonstrated in several prospective and open-label studies, in the range of 70–90% (response rate). Furthermore, numerous studies have confirmed its safety in focal dystonias. However, with repeated injections, some patients develop resistance to therapy, related to the development of blocking antibodies, although this has recently become a less common occurrence. In addition to BTX-A, other serotypes, including types B and C, are being
investigated and studies show that they are also beneficial. Many patients with CD and limb dystonias benefit from BTX alone or in combination with oral medications. Finally, it is important to emphasize that physical and supportive therapies, are essential components of a comprehensive approach to patients with dystonia.

Five-year view
Although current treatment options for dystonia remain limited, there is reason to be optimistic that new treatments will emerge over the next few years that will improve the quality of life for patients with dystonia. These are likely to fall within the categories of new surgical applications, drug discovery and gene therapy. At present, more than a dozen genetically determined dystonias have been identified, which eventually may lend themselves to gene therapy approaches. For example, an RNA interference technique has been studied in several genetic disorders, including an animal model of DYT1 dystonia. This methodology uses small segments of RNA to silence the expression of gene mutations that are responsible for abnormal protein production, such as torsinA in dystonia. Surgically, it is likely that DBS will be used in larger numbers of patients with dystonia over the coming years. As previously discussed, this has been demonstrated to be safe and effective in relatively small numbers of patients with generalized dystonia. It is very likely that DBS will become more widely used after greater experience with longer follow-up observations in these patients. Once therapeutic efficacy has been established, reduced insurance reimbursement obstacles will allow greater access to this procedure. Technological advances in DBS should also make it more practical in growing children with childhood-onset generalized dystonia. It is likely that DBS will also become used more widely in adult-onset focal dystonia, once safety and long-term efficacy is established in these disorders. New brain targets may also be applied to DBS treatment of other forms of dystonia, which are not currently being treated surgically. Finally, new methodologies to identify medications for dystonia may also be explored. As scientific insights are acquired regarding the mechanism of dystonia, new treatment options should emerge. Even in the absence of new breakthroughs in the understanding of dystonia, practical methodologies are already in place to rapidly screen compounds that may be useful to treat neurodegenerative disorders, such as Alzheimer’s disease and PD. It is possible that similar strategies may be applied to dystonia.

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Information resources
• General information on dystonia and related movement disorders.
  www.movementdisorders.org
• Professional information on dystonia, including rating scales and doses of botulinum toxin injection.
  www.mdvu.org
• Dystonia organization: Dystonia Medical Research Foundation (DMRF).
  www.dystonia-foundation.org

Key issues
• With the exception of dopa-responsive dystonia (DRD), and Wilson’s disease, the treatment of dystonia is mainly symptomatic and designed to relieve involuntary movements and improve posture and function.
• Because of an exquisite response to levodopa and the varied phenotypes in DRD, a therapeutic trial of levodopa should be considered in all patients with childhood-onset dystonia, and selected patients with adult-onset dystonia, with or without classic features of DRD.
• For patients with early-onset primary torsion dystonia, most of whom have segmental or generalized dystonia, oral medication is usually the mainstay of therapy. Among all pharmacological agents, anticholinergics are the most useful and effective, with approximately 50% of patients responding at least moderately.
• For patients with adult-onset primary torsion dystonia, in which the dystonia is usually focal, botulinum toxin therapy is generally considered to be the treatment of choice.
• Patients with dystonia may not respond to one type of therapy and multiple strategies may be necessary before an effective therapy is found. Symptomatic or secondary dystonias tend to respond less well to pharmacotherapy.
• In general, when initiating an oral medication in dystonia, the key is to start at a low dose, slowly titrate to minimize side effects and to use the lowest effective dose. All drugs should be given in divided doses throughout the day. It is also important to reassure patients of a possible delayed response and that they need to be patient while waiting for this.
• To date, sustained improvement in motor symptoms and disability have been demonstrated in a prospective controlled study of bilateral globus pallidus interna deep brain stimulation in primary generalized dystonia, whether they are DYT1 or non-DYT1 children or adult patients.
References

Papers of special note have been highlighted as:
• of interest
** of considerable interest


** Current rating scales used in the evaluation of dystonia.


** Teaching tape of how to perform the Toronto Western Spasmodic Torticollis Rating Scale.


** Good review article on medical therapy of dystonia.


Evidence-based review of medical therapy and botulinum toxin therapy in dystonia.


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www.future-drugs.com

** American Academy for Cerebral Palsy and Developmental Medicine review article on the use of intrathecal baclofen in spastic and dystonic cerebral palsy.

** Excellent review article on the mechanism of action of botulinum toxin.
113 Wohlfarth K, Kampe K, Bigalke H. Pharmacokinetic properties of different formulations of botulinum neurotoxin type A. Mov. Disord. 19(Suppl. 8), S65–S67 (2004).


Excellent electromyographic study in cervical dystonia (CD).


Truong D. Efficacy and safety of botulinum type A toxin complex (Dysport) for the treatment of benign essential blepharospasm. Parkinsonism Relat. Disord. 11(Suppl. 2), 68 (2005).


Excellent study on botulinum toxin treatment in limb disorders.


Excellent study on neurophysiology of basal ganglia in dystonia and hemiballism.


Excellent prospective study on globus pallidus interna deep brain stimulation (DBS) in primary generalized dystonia.


Excellent review article on DBS in dystonia.


Excellent article on patient selection and evaluation for DBS in dystonia.

Treatment of dystonia


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