# Current and future medical treatment in primary dystonia

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***Abstract:*** Dystonia is a hyperkinetic movement disorder, characterized by involuntary and sustained contractions of opposing muscles causing twisting movements and abnormal postures. It is often a disabling disorder that has a significant impact on physical and psychosocial wellbeing. The medical therapeutic armamentarium used in practice is quite extensive, but for many of these interventions formal proof of efficacy is lacking. Exceptions are the use of botulinum toxin in patients with cervical dystonia, some forms of cranial dystonia (in particular, blepharospasm) and writer's cramp; deep brain stimulation of the pallidum in generalized and segmental dystonia; and high-dose trihexyphenidyl in young patients with segmental and generalized dystonia. In order to move this field forward, we not only need better trials that examine the effect of current treatment interventions, but also a further understanding of the pathophysiology of dystonia as a first step to design and test new therapies that are targeted at the underlying biologic and neurophysiologic mechanisms.

***Keywords:*** botulinum toxin, deep brain stimulation, dystonia, pharmacotherapy, transcranial magnetic stimulation

## Introduction

Dystonia is characterized by involuntary, sustained and patterned contractions of opposing muscles, causing twisting movements and abnormal postures [Fahn *et al.* 1998]. It is a potentially disabling movement disorder, and reduced mobility, pain and a significant psychosocial impact are some of the consequences [Stamelou *et al.* 2011]. While dystonia can be secondary, due to for example structural lesions or neurodegenerative diseases, there is also primary dystonia, i.e. when dystonia (with or without tremor) is the only symptom, and there is no secondary cause or neurodegeneration. There is no cure for primary dystonia, partly also because its pathophysiology is still incompletely understood. Therefore, treatment is only symptomatic, aimed at decreasing the involuntary movements, correcting the abnormal posture, preventing contractures, reducing pain and ultimately attempting to improve quality of life. The current cornerstones of medical symptomatic treatment include chemodenervation with botulinum toxin injections, drug treatment with for example anticholinergics and surgical treatment such as bilateral pallidal stimulation. In addition, patients are referred for various allied healthcare interventions [Delnooz *et al.* 2009]. For some of these medical interventions there is good evidence, but for many sound scientific support is lacking [Balash and Giladi, 2004; Albanese *et al.* 2011]. The clinical heterogeneity, the existence of various subtypes, the use of insufficiently validated scales to quantify the clinical changes, the conduction of small and uncontrolled trials, and the absence of direct comparisons all complicate the evaluation of the therapeutic effect for some of the medical interventions that are commonly used [Jankovic, 2006].

We here attempt to provide a comprehensive review of medical treatment strategies in dystonia, with a focus on primary dystonia.

## Botulinum neurotoxin

Botulinum neurotoxin (BoNT) is a toxic protein produced by the bacterium *Clostridium botulinum*. It selectively blocks the cholinergic innervation of striate and smooth muscles and exocrine glands [De Boer *et al.* 2012]. BoNT injections in

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dystonia are given intramuscularly, often under electromyography (EMG) guidance, and need to be repeated every 3–6 months. Contraindications for the use of BoNT include history of neuromuscular disease, e.g. myasthenia gravis, Lambert–Eaton syndrome or motor neuron disease, and a history of hypersensitivity to BoNT, albumin or saline. BoNT injections are also contraindicated in combination with aminoglycoside, penicillamine, quinine and calcium-channel blockers as the effect of these drugs may be potentiated. As teratogenicity of BoNT is still unknown, it is advised not to use BoNT during pregnancy and lactation.

### Cervical dystonia

BoNT injections are the first-line therapy for cervical dystonia (CD). Meta-analysis of several double-blind, placebo-controlled trials have demonstrated a beneficial effect of the BoNT type A (BoNT-A) *versus* placebo on multiple domains, such as dystonia severity, pain and the patient's and physician's subjective judgement. Adverse events are usually transient and mild. The most relevant side effects, of increasing frequency with higher doses and therefore dose-limiting, are neck weakness, dysphagia, dry mouth/sore throat and voice changes/hoarseness. Others are dose-independent and include pain at the site of injection, malaise, upper respiratory infection and headache [Costa *et al.* 2005b].

BoNT also has proven long-term safety and efficacy. Several large case series have shown treatment efficacy up to 10 years, without long-term adverse effects [Blackie and Lees, 1990; Haussermann *et al.* 2004]. The occurrence of a secondary nonresponse, likely due to antibodies to BoNT or other components, was rare (1–2%) [Kessler *et al.* 1999; Haussermann *et al.* 2004; Brin *et al.* 2008]. Also primary nonresponse is seen, but reports documenting its occurrence are sparse [Truong *et al.* 2005]. A comparison of efficacy and safety between two preparations of BoNT-A, (onabotulinumtoxinA [Botox®] and rimabotulinumtoxinA [Dysport®]), for the treatment of CD showed no significant differences [Odergren *et al.* 1998; Ranoux *et al.* 2002; Costa *et al.* 2005a]. In 2005, incobotulinumtoxinA (Xeomin®), a BoNT-A drug without complexing proteins, was also shown to be effective and safe for the treatment of CD [Comella *et al.* 2011], similar to onabotulinumtoxinA [Benecke *et al.* 2005; Benecke, 2009]. A direct comparison of these three BoNT-A preparations has not been done. Time will show whether the use of incobotulinumtoxinA is more advantageous than the earlier BoNT-A. When or if it will become widely available, if the medical insurers will reimburse this new variant and most importantly whether practitioners are willing to change the preparation they have experience with, have yet to be determined.

Another BoNT serotype produced by *C. botulinum* is type B (BoNT-B). A recent meta-analysis of three multicentre double-blind, placebo-controlled trials demonstrated significant benefit, with at least 20% improvement on the total score of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at week four. Subjective rating scales also improved. Adverse events were identical to BoNT-A, but they were suggested to be more frequent with BoNT-B. Although nonsignificant, there was a larger benefit for patients resistant to BoNT-A compared with those still responding to BoNT-A [Lew *et al.* 1997; Brashear *et al.* 1999; Brin *et al.* 1999; Costa *et al.* 2005a]. Comparison of the clinical effect of BoNT-A and BoNT-B showed noninferiority for BoNT-B [Pappert and Germanson, 2008].

BoNT is thus the current gold standard for CD, and has also been proven to be superior to oral trihexyphenidyl. Prospectively, 66 CD patients were randomized to treatment with trihexyphenidyl (mean dose 16.25 mg/day) plus EMG-guided placebo injections (two sessions, 8 weeks apart) or placebo tablets plus EMG-guided BoNT-A injections (two sessions, 8 weeks apart), showing larger therapeutic effect and fewer adverse events for BoNT-A [Brans *et al.* 1996].

### Blepharospasm

There are several, often uncontrolled trials of BoNT for the treatment of blepharospasm (BSP). Recently, a multicentre randomized, double-blind and placebo-controlled trial evaluated the effect of BoNT-A (Dysport, 40, 80 and 120 MU per eye) in 123 patients with BSP. At week four, functional disability was significantly lower after treatment with BoNT-A compared with placebo. The effect was dose-related, with continued benefit up to 12 weeks for all doses, and up to 16 weeks for 80 or 120 MU per eye. Reported side effects included ptosis, blurred vision, lagophthalmos, diplopia, increased lacrimation and aggravated dry eyes [Truong *et al.* 2008]. With regards to the

long-term treatment effect, a trend towards reduced duration of symptom relief [Gill and Kraft, 2010] and a necessity to increase BoNT dose over the years were recently mentioned [Cillino *et al.* 2010]. The different BoNT preparations are similar in terms of efficacy and adverse effects [Roggenkamper *et al.* 2006; Jankovic, 2009; Wabbels *et al.* 2011].

### *Focal hand dystonia*

The use of BoNT-A to treat writer's cramp (WC) has been assessed in several placebo-controlled studies. Small patient numbers and different designs have led to inconclusive results [Yoshimura *et al.* 1992; Tsui *et al.* 1993; Cole *et al.* 1995]. In one of the best studies available, 39 WC patients were randomized to two treatment sessions with either BoNT-A or placebo injections. Seventy per cent of the BoNT-A group demonstrated an improvement, in contrast to 32% of the placebo group. Both the Writer's Cramp Rating Scale (WCRS) score and writing speed significantly improved in favour of the BoNT-A group. Side effects included hand weakness, mostly mild and transient, and pain at the injection site. After 1 year, 51% were still on BoNT treatment [Contarino *et al.* 2007].

### *Oromandibular dystonia*

BoNT treatment trials in oromandibular dystonia (OMD) have been small and/or open label [Blitzer *et al.* 1989; Hermanowicz and Truong, 1991; Van Den Bergh *et al.* 1995; Poungvarin *et al.* 1997; Tan and Jankovic, 1999; Laskawi and Rohrbach, 2001]. The largest prospective open-label study, concerning 162 patients, reported moderate to excellent improvement in almost 70% of OMD patients. The jaw-closing OMD patients responded best. Thirty-one per cent reported adverse events, mostly dysphagia and dysarthria [Tan and Jankovic, 1999]. One single, placebo-controlled and double-blind study, but including only eight OMD-CD patients, showed improvement with BoNT in three patients [Jankovic and Orman, 1987].

### *Spasmodic dysphonia*

For spasmodic dysphonia (SD), there is data from several clinical studies and meta-analyses [Wong *et al.* 1995; Brin *et al.* 1998; Whurr *et al.* 1998; Finnegan *et al.* 1999; Boutsen *et al.* 1998; Watts *et al.* 2006, 2008; Blitzer, 2010]. One double-blind, placebo-controlled study examined the effects of BoNT-A *versus* saline in 13 adductor SD patients and revealed significant effects of BoNT-A on voice quality, perceived voice improvement and acoustic measurements [Troung *et al.* 1991]. Recently, long-term effects were retrospectively evaluated in 55 patients, showing a decrease in BoNT-A dose, with increasing treatment intervals and effect duration over the years [Birkent *et al.* 2009]. The reported experience with BoNT-B is limited. Adler and colleagues reported a good effect in eight of 10 patients, lasting up to 8 weeks [Adler *et al.* 2004]. In contrast to adductor SD reports on abductor SD are limited, showing less impressive and variable results [Bielamowicz *et al.* 2001; Woodson *et al.* 2006; Blitzer, 2010].

### *Other forms of focal dystonia*

Axial dystonia is often part of generalized dystonia or segmental dystonia, but can also present as an isolated form. Owing to the involvement of long and strong muscles, BoNT might be insufficient in reducing axial dystonic symptoms. Marked to moderate effect was, however, seen in several cases presenting with primary or tardive isolated axial dystonia without severe adverse effects [Mezaki *et al.* 1994; Comella *et al.* 1998; Benecke and Dressler, 2007]. Adult-onset lower limb dystonia is a rare disorder in contrast to the more common presentation of lower limb dystonia in young patients, e.g. in DYT 1. It should therefore prompt the physician to evaluate secondary causes of dystonia. Moderate to marked improvement with BoNT is also observed in patients with rare primary lower limb dystonia [Duarte *et al.* 1995; Schneider *et al.* 2006a; Singer and Papapetropoulos, 2006; Martino *et al.* 2010; Pont-Sunyer *et al.* 2010].

In summary, treatment with BoNT-A is an effective treatment in many of the focal dystonias, with good evidence in CD and BSP, and is therefore the first-line intervention for most of the focal dystonias. Although BoNT-B has only been thoroughly evaluated in CD, a comparable effect may be expected for the other focal dystonia subtypes but this remains largely unproven. In clinical practice, BoNT can also be applied in patients with generalized dystonia as an add on to other treatment interventions for selected dystonic body segments.

## Oral drug therapy

Conventional drug treatment has been the cornerstone in dystonia treatment for many years, but BoNT has taken over its position over the last 15 to 20 years, particularly for the focal subtypes. Still, oral medication is widely used, particularly in generalized dystonia or in focal dystonias when there is an unsatisfactory response to BoNT (Table 1).

### *Anticholinergic agents*

Anticholinergic drugs block the action of acetylcholine on central muscarinic receptors. Common adverse effects include dry mouth, blurred vision, constipation, urinary retention, memory loss, hallucinations and behavioural changes. These side effects increase in frequency with age, limiting the use of anticholinergics in older patients [Gerretsen and Pollock, 2011].

In a retrospective analysis of open-label trials of initial treatment with anticholinergic agents, data from 358 primary focal and generalized dystonia patients were reviewed [Greene *et al.* 1988a]. A 'good' response, defined as a slight, moderate or marked improvement, was experienced by 40–50% of patients. There was no correlation between a good response and distribution of dystonia, sex or disease severity. Burke and colleagues reported an improvement up to 72% in a double-blind, randomized crossover study using trihexyphenidyl *versus* placebo in 31 primary segmental or generalized dystonia patients, all younger than 32 years. Again, distribution, aetiology and sex were not correlated with treatment effect [Burke *et al.* 1986]. Despite the common use in older adults, there is no controlled trial of trihexyphenidyl in older adults with dystonia.

### *GABA-mimetic agents*

Baclofen (β-parachlorophenyl GABA) is a GABA-B receptor agonist that decreases the monosynaptic and polysynaptic reflex response in afferent terminal nerves and induces muscle relaxation. Dose-related adverse effects include lethargy, dizziness, gastrointestinal complaints and urinary frequency. In addition, psychotic episodes and seizures can result from abrupt baclofen withdrawal [De Boer *et al.* 2012]. In a retrospective analysis of open-label trials, the data from 108 primary dystonia patients treated with baclofen were reviewed [Greene *et al.* 1988a, 1988b; Greene and Fahn, 1992; Greene, 1992]. A 'good' response, defined as a slight, moderate or marked improvement, was seen in 20% of the patients. BSP patients responded best (30%), in contrast to generalized dystonia (13%) and CD (11%), although these differences were not significant. Baclofen can also be given intrathecally. At present, this is mainly considered in patients with the combined presence of spasticity and dystonia (secondary to perinatal asphyxia for example) or in status dystonicus. It has also been used in some cases of primary dystonia. Uncontrolled case series suggest that intrathecal baclofen results in an improvement of mainly axial and limb dystonia [Diederich *et al.* 1997; Ford *et al.* 1998; Manji *et al.* 1998; Walker *et al.* 2000; Hou *et al.* 2001; Jaffe and Nienstedt, 2001; Dykstra *et al.* 2005; Teive *et al.* 2005; Grosso *et al.* 2012]. However, at present, there is insufficient evidence to support the use of intrathecal baclofen in primary dystonia or primary status dystonicus.

Benzodiazepines act by potentiating neural inhibition mediated by GABA. Adverse effects of benzodiazepine treatment include sedation and confusion. Several variants have been evaluated in primary dystonia, mainly in CD, but none in a controlled setting. In the above-mentioned report by Greene and colleagues [Greene *et al.* 1988a, 1988b], 16% of 115 patients responded well to clonazepam. The response rate for BSP and CD was 23% and 21%, respectively, while this was only 6% for generalized dystonia; again, these differences were not significant. The effect was not correlated with sex, aetiology, age at onset or severity. There are also reports of marked relief of dystonic symptoms after (intravenous) diazepam [Ahmad and Meeran, 1979; Ziegler, 1981; Francis, 1983]. In the same retrospective chart review by Greene and colleagues, anticholinergics were, however, found to be significantly more effective than GABA mimetics in CD and BSP [Greene *et al.* 1988a].

### *Dopamine-altering agents*

All patients with an early onset dystonia, particularly in the case of limb onset, should receive a trial of levodopa given the possibility of dopa-responsive dystonia (DRD), one of the dystonia-plus disorders. While in DRD levodopa leads to a considerable improvement [Steinberger *et al.* 2000; Hwang *et al.* 2001; Nutt and Nygaard, 2001; Schneider *et al.* 2006b], the effect in primary dystonia is often less impressive. Reviewing 214 cases, 39% of generalized dystonia patients

**Table 1.** Oral drugs used in the treatment of dystonia.

| | Dose | Adverse effects [De Boer *et al.* 2012] |
|---|---|---|
| **Commonly used** | | |
| *Anticholinergics* | | |
| Trihexyphenidyl | Gradually increase to 12 mg in 4 weeks, up to 60–100 mg q.d. [Jankovic, 2006] | Dry mouth, blurred vision, constipation, urinary retention, confusion, memory loss, hallucinations, behavioural changes |
| *GABA-mimetics* | | |
| Baclofen | Gradually increase to 30 mg in 1 week, up to 40–180 mg q.d. [Greene, 1992] | Lethargy, dizziness, gastrointestinal complaints, urinary frequency |
| Clonazepam | Gradually increase in 2–4 weeks, up to 1.5–12 mg q.d. [Greene *et al.* 1988a] | Drowsiness, dizziness, ataxia, confusion |
| *Dopaminergic agents* | | |
| Levodopa (DRD) | Start with 100 mg levodopa + 25 mg decarboxylase inhibitor, increase up to 1000 mg. When after 1 month no effect, stop and reconsider diagnosis DRD [Jankovic, 2006] | Dyskinesia, sleepiness, orthostatic hypotension, nausea, gastrointestinal symptoms, hallucinations, behavioural changes |
| **Rarely used** | | |
| Tetrabenazine | Gradually increase in 7 weeks, up to 100 mg q.d., starting with 12.5 mg [Kenney *et al.* 2007] | Drowsiness, Parkinsonism, depression, akathisia |
| Apomorphine | 10–50 mg continuously SC, sometimes in combination with levodopa / lisuride [Langkafel *et al.* 1991] | Sedation, confusion, hallucinations, skin irritation |
| Lisuride | 0.4 to 5–12 mg q.d [Bassi *et al.* 1982; Quinn *et al.* 1985] | Dyskinesia, sleepiness, orthostatic hypotension, nausea, gastrointestinal symptoms, hallucinations, behavioural changes |
| Bromocriptine | 18–150 mg/day (mean 72.5 mg) [Stahl and Berger, 1981; Newman *et al.* 1985] | Nausea, vomiting, constipation, headache, sedation, dizziness |
| Clozapine | Gradually increase by 12.5–25 mg q.d., up to 300 mg q.d. [Karp *et al.* 1999] | Sleepiness, tachycardia, dizziness, constipation, granulocytopenia |
| Olanzapine | Gradually increase by 2.5 mg q.d., up to 15 mg q.d. [Lin and Chang, 2004] | Sleepiness, tachycardia, dizziness, constipation, granulocytopenia, weight gain |
| Tiapride | Start with 100 mg t.i.d. IV, continue with equal oral dose, up to 500 mg q.d. [Arlazoroff *et al.* 1991] | Hyperprolactinemia, sleepiness, dizziness, behavioural changes, headache, Parkinsonism |
| Risperidone | Start with 2 mg q.d., increase daily up to 8 mg q.d. [Wohrle *et al.* 2003] | Depression, weight gain, Parkinsonism, headache, insomnia |
| Orphenadrine | NA [Jacob, 1962] | Dry mouth, blurred vision, constipation, urinary retention, confusion, memory loss, hallucinations, behavioural changes |
| Haloperidol | Gradually increase by 0.5 mg q.d. to 1.5–14 mg q.d. [Gilbert, 1972] | Emotional deprivation, dystonia, Parkinsonism |
| Diphenidramine | Start with 50 mg q.i.d., increase up to 400 mg q.d. [Truong *et al.* 1995] | Somnolence, dizziness, dry mouth, tachycardia, urinary retention, constipation |
| Mexiletine | Start with 200 mg q.d., increase up to 450–1200 mg q.d. [Ohara *et al.* 1998; Lucetti *et al.* 2000] | Dizziness, heartburn, nausea, nervousness, trembling, unsteadiness |
| Chlorzoxazone | NA [Strang, 1967] | Dizziness, malaise, nausea, vomiting, liver dysfunction |
| Carbamazepine | Gradually increase up to 200–1200 mg q.d., starting with 200 mg q.d. [Geller *et al.* 1976] | Leukopenia, dizziness, ataxia, sleepiness, nausea, vomiting, skin rash |
| Levetiracetam | Gradually increase up to 1000 mg b.i.d. / 1500 mg t.i.d., starting with 500 mg q.d. [Zesiewicz *et al.* 2004; Sullivan *et al.* 2005; Yardimci *et al.* 2006] | Asthenia, sleepiness, ataxia, behavioural changes, depression, amnesia |

b.i.d., twice a day; DRD, dopa-responsive dystonia; IV, intravenously; NA, not available; q.d., per day; q.i.d., four times a day; SC, subcutaneous; t.i.d., three times a day.

showed marked to moderate improvement on levodopa, followed by CD (27%) and cranial dystonia (6%). No effect was found in WC patients [Lang, 1988].

Various dopamine-antagonist agents have been studied, mainly in uncontrolled trials. Given the potential side effects such as acute or tardive dystonia, their use is often discarded in dystonia patients. The overall picture is that of a variable effect. Tetrabenazine was shown to be effective in various types of generalized and focal dystonia in a small, double-blind crossover study [Jankovic, 1982]. Recently, a retrospective chart review was performed on patients treated with tetrabenazine for a variety of hyperkinesias, including dystonia ($n$ = 132), but without further details on the subtypes of dystonia. Marked-to-moderate improvement was seen in 67% and 70% after 3 and 6 months, respectively. Common adverse effects included drowsiness, Parkinsonism, depression and akathisia [Kenney *et al.* 2007]. These results confirm earlier reports [Jankovic and Orman, 1988; Jankovic and Beach, 1997]. In small series, symptomatic relief, albeit variable, has also been reported for phenothiazines, pimozide and haloperidol [Gilbert, 1972; Lang, 1988].

Clozapine is a dibenzodiazepin derivative, atypical antipsychotic agent that predominantly blocks the dopamine D4 receptor [De Boer *et al.* 2012]. An open-label study in five patients with generalized dystonia and Meige syndrome revealed significant improvements upon clozapine treatment, with dose-limiting adverse effects in one patient [Karp *et al.* 1999]. More recently, two OMD patients reported marked improvement with clozapine [Hanagasi *et al.* 2004]. A third open-label report on 10 CD patients demonstrated subjective improvement and a significant decrease in the TWSTRS pain score and rate of clonic movements; there were however no significant effects for the severity and disability TWSTRS subscores [Burbaud *et al.* 1998]. In contrast, another open-label trial of clozapine in five CD patients failed to demonstrate benefit after 3–12 weeks of treatment [Thiel *et al.* 1994]. On top of these rather contrasting results from uncontrolled and small studies, the use of clozapine in practice may be limited by the necessity to regularly monitor hematologic parameters. Other atypical neuroleptics, such as olanzapine, risperidone and tiapride, have occasionally demonstrated marked to good improvement as well [Arlazoroff *et al.* 1991; Zuddas and Cianchetti, 1996; Grassi *et al.* 2000; Wohrle *et al.* 2003; Lin and Chang, 2004].

Dopamine receptor agonists (e.g. bromocriptine, apomorphine, amantadine and lisuride) have also been tried in dystonia. In several studies reviewed by Lang, a variety of response rates were found: generalized dystonia improved with a range of 18–50% for several dopamine receptor agonists (no studies on generalized dystonia and amantadine), and a comparable broad range was found for cranial dystonia (0–62%) and CD (6–39%). Adverse effects led to frequent withdrawal and symptomatic decline was seen in nearly 25% of patients. The best effect was suggested to be obtained with apomorphine [Lang, 1988]. A small double-blind placebo-controlled trial in CD patients showed no effect for amantadine [West, 1977]. Yet, overall the data are far from conclusive. In a double-blind, placebo-controlled study that came out after this review and in which seven patients (six of whom with primary generalized and focal dystonia) were given apomorphine intravenously, five patients improved following injection, again suggesting that dopamine agonists could be an effective treatment in various subtypes of dystonia, but more work is needed [Langkafel *et al.* 1991].

Many patients with dystonia need a combination of several drugs and other treatments to obtain sufficient symptomatic relief. Marsden and colleagues proposed a triple therapy, known as the 'Marsden cocktail', consisting of a dopamine antagonist (tetrabenazine), a dopamine-blocking drug (pimozide) and, in patients with severe dystonia, the addition of an anticholinergic agent. Seventy-five per cent of the adults with severe axial dystonia experienced substantial improvement from this drug combination [Marsden *et al.* 1984].

Various other oral pharmacological agents, such as carbamazepine, levetiracetam, orphenadrine, chlorzoxazone, diphenidramine and mexiletine have been reported to give some symptomatic relief in dystonia patients, but these observations should be labelled as anecdotal [Jacob, 1962; Strang, 1967; Geller *et al.* 1976; Ten Houten *et al.* 1984; Truong *et al.* 1995; Ohara *et al.* 1998; Lucetti *et al.* 2000; Zesiewicz *et al.* 2004; Sullivan *et al.* 2005; Yardimci *et al.* 2006; Hering *et al.* 2007].

In summary, various oral drugs are being used in the treatment of primary dystonia. There is a remarkable absence of sufficiently large,

**Table 2.** Advised treatment options per dystonia subtype.

| | First-line treatment | Add-on treatment | Treatment in refractory cases |
|---|---|---|---|
| Cervical dystonia | BoNT | Trihexyphenidyl<br>Baclofen<br>Clonazepam | Tetrabenazine<br>Pallidal DBS<br>Selective peripheral denervation |
| Blepharospasm | BoNT | Baclofen<br>Clonazepam | DBS<br>Myectomy |
| Oromandibular dystonia | BoNT | Baclofen<br>Clonazepam<br>Tetrabenazine | |
| Focal hand dystonia | BoNT | | |
| Spasmodic dystonia | BoNT | | Myectomy |
| Generalized dystonia | Trihexyphenidyl | BoNT<br>Baclofen<br>Clonazepam | Pallidal DBS<br>Tetrabenazine / Neuroleptics<br>Intrathecal baclofen |

BoNT, botulinum neurotoxin; DBS, deep brain stimulation.

randomized controlled trials (RCTs). Most data come from large, retrospective case series or medium-sized, prospective open-label studies. As sound evidence for most of the oral pharmacological agents is lacking, there is no consensus about this line of treatment. At present, anticholinergics seem to be the most promising group, followed by the GABA mimetics. The order in which oral drugs should be started, the maximum dose at which they can or should be given, and when or how to combine different drugs are still determined by the practitioner's personal experience. Table 2 indicates how we use the drugs discussed above per dystonia subtype.

## Surgical treatment

For many patients with generalized dystonia, and also for some with focal dystonia, all pharmacological options outlined above offer insufficient relief. Surgical treatment may then be considered. Surgery in dystonia has a long history and over the years several procedures have been performed: selective peripheral denervation (typically in CD, Bertrand procedure), myectomy (SP and BSP) and stereotactic lesioning of the basal ganglia or thalamus. The current surgical treatment of choice in most cases, however, is deep brain stimulation (DBS).

### *Deep brain stimulation*

DBS is an established treatment of Parkinson's disease and essential tremor. DBS alters neuronal discharge or axonal propagation (or both) in the target structure that is stimulated. The exact mechanism by which this effect occurs, is still unclear. Advantages over stereotactic surgery are adaptability of stimulation and reversibility in case of adverse effects [Katayama *et al.* 2003]. Kupsch and colleagues reported a randomized multicentre double-blind series of 40 patients with primary segmental dystonia and primary generalized dystonia using bilateral pallidal DBS or sham stimulation. After 3 months, patients receiving DBS showed almost 40% improvement in BFMDRS movement and disability scores, increasing further after 6 months [Kupsch *et al.* 2006]. A second randomized, double-blind multicentre trial of bilateral pallidal DBS in 22 primary generalized dystonia patients disclosed similar effects [Vidailhet *et al.* 2005]. There is limited data on the (very) long-term effects, though clinical improvement is seen up to 6 years [Vidailhet *et al.* 2007; Loher *et al.* 2008]. Longer follow-up data will become available over the next few years.

Patients with focal rather than generalized dystonia appear to benefit from DBS as well. Most publications concern bilateral pallidal stimulation

in CD. One prospective, single-blinded multicentre trial has been reported, in which 10 patients with chronic and therapy-resistant CD were evaluated. The TWSTRS severity score improved by 44% after 12 months, and TWSTRS disability and pain subscores by 64% and 65%, respectively. Also general health, physical functioning and depression improved; only mild or transient adverse effects were seen, comparable to generalized dystonia [Kiss *et al.* 2007]. A long-term effect up to 3 years after surgery has been reported in smaller series of CD patients [Bittar *et al.* 2005; Hung *et al.* 2007; Huh *et al.* 2010; Pahapill and O'Connell, 2010].

Patients with cranio-cervical dystonia, e.g. Meige syndrome, have also been treated with DBS. Twelve patients with Meige syndrome were evaluated retrospectively up to 78 months, reporting a mean BFMDRS improvement of 45% at short-term follow up and 53% at long-term follow up, without clear differences between eye, mouth or speech subscores [Reese *et al.* 2011]. Comparable results were found in other series, also reporting reversible stimulation-induced bradykinesia in previously nondystonic limbs after prolonged pallidal DBS [Ostrem *et al.* 2007; Ghang *et al.* 2010].

There are limited data with regard to DBS targeting other sites than the internal pallidum. Several series describe DBS of the subthalamic nucleus (STN) in dystonia [Mundinger, 1977; Andy, 1983; Kleiner-Fisman *et al.* 2007; Moll *et al.* 2008; Cho *et al.* 2009; Allert *et al.* 2010; Pahapill and O'Connell, 2010]. A prospective, single-blinded pilot study reported on nine CD patients with STN-DBS, improving 37% on the TWSTRS total score at 12 months. Quality of life measures also improved and STN-DBS caused no cognitive side effects or Parkinsonism [Ostrem *et al.* 2011]. The posterior part of the ventrolateral thalamic nucleus has also been targeted [Vercueil *et al.* 2001]. Two out of a series of three patients with primary generalized dystonia experienced a mild-to-moderate improvement of limb dystonia, whereas axial symptoms remained unchanged.

DBS-related adverse effects can be caused by the surgical procedure itself, the implanted hardware or brain stimulation. Speech abnormalities, referred to as dysarthria, dysphonia or stuttering, are reported frequently. Other side effects include perioral tingling, poor coordination and slowness, akinesia and bradykinesia, gait difficulties, paresthesias, abnormalities of posture, laughter and lethargy [Tagliati *et al.* 2011]. Two suicides have been reported in patients with dystonia after DBS, but both patients had symptoms of depression before DBS [Foncke *et al.* 2006]. We are currently left uninformed about the potential long-term adverse effects of DBS in dystonia.

Several factors may contribute to a favourable outcome of DBS in dystonia. Several retrospective studies identified young age and short disease duration as positive predictors [Coubes *et al.* 2004; Alterman and Snyder, 2007; Vasques *et al.* 2009; Andrews *et al.* 2010; Isaias *et al.* 2011]. The debate on the influence of disease duration in generalized dystonia is, however, ongoing, as well on the predictive factors in CD patients [Hung *et al.* 2007; Valldeoriola *et al.* 2010]. Previously, there were reasons to believe that a mutation in the DYT1 gene underlying generalized dystonia also withheld a more favourable response to DBS [Borggraefe *et al.* 2008], but this has not been replicated by others [Coubes *et al.* 2004; Vidailhet *et al.* 2005, 2007; Kupsch *et al.* 2006].

Despite the good evidence to support DBS in therapy-resistant dystonia, other surgical procedures are still used. These procedures (e.g. thalamotomy in CD and WC; peripheral denervation in CD) seem to be performed most in Asian countries where BoNT treatment is often not reimbursed by the medical insurers. Myectomy is still regularly used in BSP when patients are refractory to BoNT.

### *Peripheral surgical denervation in CD*

Peripheral surgical denervation gives similar improvement in objective and subjective ratings as pallidal DBS [Huh *et al.* 2010]. There are different peripheral denervation procedures: posterior ramisectomy [Bertrand *et al.* 1978] with or without myotomy; anterior cervical rhizotomy; and microvascular decompression of the spinal accessory nerve, are used for focal and segmental dystonias. A direct comparison of these methods is lacking. Moderate to excellent improvement in head position and pain was reported in patients treated with posterior ramisectomy, even in the long term. Persistent C2-distributed dysesthesias, shoulder girdle weakness and muscle reinnervation-related pain are common adverse effects [Munchau *et al.* 2001; Cohen-Gadol *et al.* 2003]. Recently, a new method of peripheral denervation was applied, obtaining similar benefit but with less sensory disturbances [Taira and Hori, 2003a]. Results of intradural procedures are highly

variable, ranging from 60% to 90% postoperative improvement [Hamby and Schiffer, 1969, 1970; Arseni and Maretsis, 1971; Fabinyi and Dutton, 1980; Colbassani and Wood, 1986; Speelman *et al.* 1987; Gauthier *et al.* 1988; Hernesniemi and Keranen, 1990]. The two main concerns are the sustainment of the effect and the adverse events. The question is which CD patients to consider suitable for this type of surgery. The direction of CD seems an important element here. The risk-to-benefit ratio is perhaps poorest in antecollis, and one would at present consider DBS in such patients first (see above). A crucial factor here is the experience of the surgical team and only a couple of centres in the world meet this criterion.

### *Myectomy*

Surgical treatment can be considered in BoNT-unresponsive BSP. In recent years, various forms of myectomy or frontal suspension have been reported on [Nicoletti *et al.* 2009; Patil and Foss, 2009]. Retrospective studies report marked improvement or resolution of BSP and increased effect of BoNT with myectomy or single frontal suspension, with long-term benefit [Chapman *et al.* 1999; Grivet *et al.* 2005; Wabbels and Roggenkamper, 2007; Georgescu *et al.* 2008]. Also in SD, different types of myectomy of the thyroarytenoid muscle are performed [Remacle *et al.* 2005; Tsuji *et al.* 2006; Kim *et al.* 2008; Nakamura *et al.* 2008]. The therapeutic effect and adverse events depend on the type of surgery. Limited myectomy produces less benefit with more frequent symptom recurrence after 6 months necessitating BoNT, while complete myectomy or myectomy with neurectomy leads to a longer lasting improvement, but with adverse breathing impairment. Facial nerve lysis in BSP and recurrent laryngeal nerve section in SD have been abandoned since the arrival and efficacy of BoNT [Ludlow, 2009].

### *Stereotactic surgery*

Thalamotomies have been performed in patients with generalized dystonia and CD, using the Voa, Vop, Vim, subthalamic region, centromedian nucleus and pulvinar as targets [Hassler and Dieckmann, 1970; Krayenbuhl and Siegfried, 1972; Mundinger *et al.* 1972; Andrew *et al.* 1974, 1983; Gros *et al.* 1976; Cardoso *et al.* 1995; Imer *et al.* 2005]. Results have been variable, with improvement rates between 15% to 25% of patients; rates were highest for those with primary dystonia. Serious complications were found in a quarter of those who received surgery [Cooper, 1976; Tasker *et al.* 1988]. More recently, thalamotomy was performed in 12 patients with focal hand dystonia (FHD; WC and musician's cramp), reporting significant improvement of the WCRS directly after surgery. Two patients relapsed 5 months after surgery [Taira and Hori, 2003b]. With regard to pallidotomy, only smaller case series of anterior or posteroventral pallidotomy in primary (generalized) dystonia patients have been published with highly variable results [Iacono *et al.* 1996; Lozano *et al.* 1997; Ondo *et al.* 1998]. Frequently reported adverse effects included speech problems and cognitive deficits [Hariz *et al.* 2011]. Appreciating the limitation caused by methodological differences between the two surgical groups, pallidotomy exhibits significantly better long-term outcomes than thalamotomy [Yoshor *et al.* 2001].

A direct comparison of DBS *versus* stereotactic surgery has not been done, and even an indirect comparison is difficult as no randomized, placebo-controlled, double-blind trials for the latter exist. Despite the preferable use of DBS in present practice, one could question the current place of stereotactic surgery. It can be argued that the effectiveness of stereotactic surgery is *under*estimated as concerning literature dates from a period of surgical development. On the other hand, results may be *over*estimated due to the absence of RCTs. Second, stereotactic surgery is free of limitations concerning hardware and programming issues as seen with DBS, possibly leading to lower costs. Overall, the use of stereotactic surgery may be up for debate, especially with the arrival of studies on modern stereotactic techniques [Gross, 2008].

In summary, pallidal DBS is proven to be efficacious in primary generalized dystonia. Evidence also suggests beneficial effects for CD and possibly for cranial dystonia. The long-term effects and side effects of pallidal DBS, and proof of effect of DBS in other types of dystonia and perhaps other stimulation sites have to be addressed more thoroughly in future studies. Given the level of evidence, current experience and assumed lower rate of adverse events, DBS is at present the preferred technique above stereotactic surgery. Also, selective peripheral denervation and myectomy may, when performed in experienced centres, be effective substitutes for DBS for some focal subtypes

that respond insufficiently to BoNT and oral pharmacotherapy.

## Noninvasive neurostimulation

Despite the limited understanding of the pathophysiology of primary dystonia, three mechanisms are thought to be fundamental contributors. A loss of inhibition on several levels of the central nervous system has been demonstrated, leading to unnecessary contractions of more muscles than required [Hallett, 2011]. Other evidence suggests that somatosensory processing and sensorimotor integration are altered [Hallett, 2011], possibly as a consequence of underlying maladaptive synaptic plasticity [Quartarone *et al.* 2008]. Alteration of these abnormal activity patterns may serve as new therapeutic targets for noninvasive neurostimulation. Although still in the experimental stage, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are mentioned here.

### *Transcranial magnetic stimulation*

TMS is a noninvasive method to depolarize or hyperpolarize neurons. It uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field. This can cause activity in targeted (and remote) areas of the brain, allowing the functioning and interconnections of the brain to be studied or temporarily altered.

To the best of the authors' knowledge, only nine reports on TMS exist, mainly all on FHD patients [Siebner *et al.* 1999a, 1999b; Bhidayasiri and Bronstein, 2005; Murase *et al.* 2005; Allam *et al.* 2007; Borich *et al.* 2009; Havrankova *et al.* 2010; Huang *et al.* 2010; Kranz *et al.* 2010]. Testing low-intensity repetitive TMS (rTMS) in separate sessions over the primary motor cortex, supplementary motor area, and dorsal premotor cortex (PMd) in nine dystonic WC patients, Murase and colleagues found that only PMd stimulation improved handwriting. The duration of the effect was left unmentioned. Patients received rTMS three times, each session over a different site with an interval of 1 week [Murase *et al.* 2005]. Borich and colleagues reported a similar improvement after PMd stimulation lasting for 5–10 days in a small part of the study population [Borich *et al.* 2009]. In contrast, TMS over the primary motor cortex in 16 WC patients demonstrated no significant effect [Siebner *et al.* 1999a, 1999b]. Interestingly, a case study with rTMS over the left PMd in neck and limb dystonia showed improvement of neck but not of limb symptoms [Allam *et al.* 2007]. Others have tried to modulate sensory input. In a single blinded, partial crossover randomized trial, 11 WC patients were treated with rTMS over the contralateral primary sensory cortex for 5 consecutive days. The largest effect was found in an objective handwriting measure (31%) directly after the treatment, lasting at least for 3 weeks [Havrankova *et al.* 2010]. TMS over the anterior cingulate cortex in BSP (12 patients) resulted also in subjective and objective improvement, scored as the percentage of improvement in blink frequency, time of eye closure and the number of sustained blinks. Effects lasted at least until 3 hours after rTMS [Kranz *et al.* 2010].

### *Transcranial direct current stimulation*

tDCS works by sending constant, low direct current through two surface electrodes. When these electrodes are placed in the region of interest, the current induces intracerebral current flow altering neuronal excitability and leading to alteration of brain function. Four reports on tDCS were found, all reporting on FHD (especially musician's cramp). In a randomized, double-blind, sham-controlled study, 12 unilateral dystonic WC patients were investigated. Cathodal or placebo stimulation of the contralateral motor cortex was used in three sessions within 1 week without clinical benefit or restoration of handwriting kinematics and cortical inhibition. Remarkably, subjective improvement was seen in the sham group [Benninger *et al.* 2011]. A placebo-controlled, double-blinded study on professional guitarists with musician's dystonia using cathodal tDCS over the primary motor cortex contralateral to the affected hand, did not improve fine motor control. However, in one guitarist, suffering from arm dystonia (the other guitarists suffered from hand dystonia), motor control did improve [Buttkus *et al.* 2010b]. A beneficial effect of tDCS as add on with sensorimotor retraining in nine pianists could also not be established [Buttkus *et al.* 2010a, 2010b]. Despite the absence of improvement after single-session tDCS, future stimulation protocols have to be optimized and may reveal a more favourable effect in the future.

In summary, as more insight in the pathophysiology of primary dystonia is gained, noninvasive neurostimulation may be a promising new treatment option. Future studies have to be performed to

identify the best cerebral targets and stimulation protocols that will lead to lasting and objective improvement of dystonic symptoms. This might be translated to a more continuous, yet invasive form of cortical stimulation. Already (pre)motor cortical stimulation is being piloted in primary and secondary dystonia patients with moderate effect [Romito *et al.* 2007; Messina *et al.* 2011; Lalli *et al.* 2012].

## Treatment of common complications

### *Pain*

With a prevalence ranging between 67% and 75%, pain is one of the most frequently forwarded symptoms in dystonia. It does not invariably correlates with disease severity. Often pain sensation is aggravated by additional low mood [Kuyper *et al.* 2011; Stamelou *et al.* 2011]. Other than pain reduction by BoNT treatment [Costa *et al.* 2005a], no other pharmacological agents have been studied for their specific effect on pain in dystonia. Routinely, traditional analgesics are often given. Reduction of painful dystonic spasms with BoNT and addressing aggravating comorbidities are thus essential in the treatment of dystonic pain.

### *Mood*

Depression is a highly prevalent comorbidity in dystonia, either secondary to dystonic symptoms and its chronicity or as a primary disease feature perhaps [Kuyper *et al.* 2011; Stamelou *et al.* 2011]. In addition to the well-known treatment with antidepressants or cognitive therapy [Cipriani *et al.* 2009; Jakobsen *et al.* 2011a, 2011b], depressive complaints may be indirectly and partly reduced by treatment aimed at reducing dystonia severity. Treatment with BoNT is suggested to relief low mood in several subtypes of primary dystonia and also DBS can lead to mild improvement of depression [Hariz *et al.* 2011; Jahanshahi *et al.* 2011; Jahanshahi and Marsden, 1992; Ochudlo *et al.* 2007; Slawek *et al.* 2007]. In contrast, worsening of a mood disorder and even suicide have also been reported after DBS. As dystonic symptoms were evidently reduced by adequate therapy in these cases, severity of dystonia does not necessarily correlate with symptoms of depression [Foncke *et al.* 2006; Kuyper *et al.* 2011; Ostrem *et al.* 2011].

### *Orthopaedic and neurological complaints*

Other common complications in mainly CD patients and in patients with generalized dystonia are orthopaedic and neurological complications. These include premature (cervical) spine degeneration, spondylosis, disc herniation, vertebral subluxations and fractures, radiculopathies and myelopathy. Negative predictors are generalization of dystonic symptoms, age and disease severity. In addition to the premature occurrence of degenerative spinal complications [Konrad *et al.* 2004; Guettard *et al.* 2012], the spine is affected at higher cervical levels (C2–C5) in dystonia in contrast to the middle and lower cervical spine involvement (C5–C7) in aging [Loher *et al.* 2006]. There is no consensus about the optimal surgical procedure for these spinal complications caused by dystonia. Several types of spinal surgery (laminectomy, anterior(–posterior) decompression with intercorporal fusion) with or without immobilization (halo-vest, hard or soft collars depending on the type of spinal surgery) may ameliorate symptoms. One has to be alert to secondary problems as spinal instability, pseudarthrosis and adjacent-level disease [Konrad *et al.* 2004; Wong *et al.* 2005; Loher *et al.* 2006]. Spinal surgery in dystonia is further complicated by continuous mechanical forces due to dystonic posture, which can be alleviated by preoperative and postoperative use of BoNT or DBS [Traynelis *et al.* 1992; Adler *et al.* 1996; Racette *et al.* 1998; Krauss *et al.* 2002; Tonomura *et al.* 2007]. Also scoliosis or contractures of ankle, wrist or hand are commonly seen. Despite limited evidence, standard physiotherapy, BoNT or serial casting may be useful in reducing symptoms of the latter. Evaluation of the treatment of scoliosis in dystonia is lacking [Singer *et al.* 2004; Olver *et al.* 2010].

## Conclusion

We have here provided an overview of the medical treatment options in primary dystonia. A summary of the advised treatments options per dystonia subtype is given in Table 2. It is clear that only some of the medical treatment options have been evaluated through properly conducted studies and thus that levels of evidence for many interventions are low. Choosing the best treatment strategy, especially when the dystonic symptoms are refractory to first-line treatment, is thus often based on the physician's opinion and experience, and our Table 2 should also be regarded as such. In addition to the treatment of the dystonia, attention to and treatment of frequently seen nonmotor complications, such as pain and depression, is crucial [Stamelou *et al.* 2011], as well as of secondary orthopaedic and neurological complications, such

as those inflicted by cervical spinal degeneration. A systematic review of the allied healthcare interventions that can be considered in dystonia patients has recently been published [Delnooz *et al.* 2009]. Further understanding of the pathophysiology of dystonia will lead to the development of more mechanism-based interventions, of which repetitive TMS over the premotor cortex in WC is a preliminary example.

## Search

For the literature search, we focused on primary dystonia. Therapies we included were pharmacological therapies, peripheral denervation, myectomy, stereotactic surgery and (noninvasive) neurostimulation. Studies could be RCTs, patient–control studies (retrospective and prospective) and case series or single case reports. When going through the various studies, only those that included a report on clinical outcome, either objectively (rating scales) or subjectively, were selected. We searched the database from 1950 to February 2012; only English publications were selected. PubMed and *The Cochrane Library* were searched in February 2012. The medical subject heading (MeSH) and free texts search terms used to identify relevant reports were 'dystonia' OR 'dystonic disorder' AND 'pharmacological therapy' OR 'anticholinergics' OR 'baclofen' OR 'benzodiazepines' OR 'tetrabenazine' OR 'dopamine' OR 'clozapine' OR 'botulinum toxin' OR 'deep brain stimulation' OR 'thalamotomy' OR 'pallidotomy' OR 'stereotactic surgery' OR 'transcranial magnetic stimulation' OR 'transcranial direct current stimulation' OR 'myectomy' OR 'peripheral denervation' OR 'motor cortex stimulation'. Furthermore, cross-references were evaluated and the authors also searched their personal literature database.

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