

# Current and future medical treatment in primary dystonia

Cathérine C.S. Delnooz and Bart P.C. van de Warrenburg

**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 chemodeneration 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

*Ther Adv Neurol Disord*

(2012) 5(4) 221–240

DOI: 10.1177/  
1756285612447261

© The Author(s), 2012.  
Reprints and permissions:  
[http://www.sagepub.co.uk/  
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:  
**Bart P.C. van de Warrenburg, MD, PhD**  
Radboud University  
Nijmegen Medical Centre,  
Department of Neurology,  
Donders Institute for  
Brain, Cognition and  
Behaviour, Centre for  
Neuroscience (943),  
PO Box 9101, 6500 HB,  
Nijmegen, the Netherlands  
[b.vandewarrenburg@  
neuro.umcn.nl](mailto:b.vandewarrenburg@neuro.umcn.nl)

**Cathérine C.S. Delnooz, MD**  
Radboud University  
Nijmegen Medical Centre,  
Department of Neurology,  
Donders Institute for  
Brain, Cognition and  
Behaviour, Centre for  
Neuroscience, the  
Netherlands

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<sup>®</sup>] and rimabotulinumtoxinA [Dysport<sup>®</sup>]), 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<sup>®</sup>), 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; Pongvarin *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 [Truong *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 ( $\beta$ -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 <i>et al.</i> 2012]
<b>Commonly used</b>		
<i>Anticholinergics</i>		
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
<i>GABA-mimetics</i>		
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 <i>et al.</i> 1988a]	Drowsiness, dizziness, ataxia, confusion
<i>Dopaminergic agents</i>		
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
<b>Rarely used</b>		
Tetrabenazine	Gradually increase in 7 weeks, up to 100 mg q.d., starting with 12.5 mg [Kenney <i>et al.</i> 2007]	Drowsiness, Parkinsonism, depression, akathisia
Apomorphine	10–50 mg continuously SC, sometimes in combination with levodopa / lisuride [Langkafel <i>et al.</i> 1991]	Sedation, confusion, hallucinations, skin irritation
Lisuride	0.4 to 5–12 mg q.d [Bassi <i>et al.</i> 1982; Quinn <i>et al.</i> 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 <i>et al.</i> 1985]	Nausea, vomiting, constipation, headache, sedation, dizziness
Clozapine	Gradually increase by 12.5–25 mg q.d., up to 300 mg q.d. [Karp <i>et al.</i> 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 <i>et al.</i> 1991]	Hyperprolactinemia, sleepiness, dizziness, behavioural changes, headache, Parkinsonism
Risperidone	Start with 2 mg q.d., increase daily up to 8 mg q.d. [Wohrle <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 1998; Lucetti <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 2004; Sullivan <i>et al.</i> 2005; Yardimci <i>et al.</i> 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 Baclofen Clonazepam	Tetrabenazine Pallidal DBS Selective peripheral denervation
Blepharospasm	BoNT	Baclofen Clonazepam	DBS Myectomy
Oromandibular dystonia	BoNT	Baclofen Clonazepam Tetrabenazine	
Focal hand dystonia	BoNT		
Spasmodic dystonia	BoNT		Myectomy
Generalized dystonia	Trihexyphenidyl	BoNT Baclofen Clonazepam	Pallidal DBS Tetrabenazine / Neuroleptics 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; Valdeoriola *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 *underestimated* as concerning literature dates from a period of surgical development. On the other hand, results may be *overestimated* 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 correlate 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 relieve 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 intercorporeal 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 'tetraabenazine' 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.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Conflict of interest statement

BvdW has received research support from Ipsen Pharmaceuticals in the past.

### References

Adler, C.H., Bansberg, S.F., Krein-Jones, K. and Hentz, J.G. (2004) Safety and efficacy of botulinum toxin type B (Myobloc) in adductor spasmodic dysphonia. *Mov Disord* 19: 1075–1079.

Adler, C.H., Zimmerman, R.S., Lyons, M.K., Simeone, F. and Brin, M.F. (1996) Perioperative use of botulinum toxin for movement disorder-induced cervical spine disease. *Mov Disord* 11: 79–81.

Ahmad, S. and Meeran, M.K. (1979) Treatment of spasmodic torticollis with diazepam. *Br Med J* 1: 127.

Albanese, A., Asmus, F., Bhatia, K.P., Elia, A.E., Elibol, B., Filippini, G. *et al.* (2011) EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol* 18: 5–18.

Allam, N., Brasil-Neto, J.P., Brandao, P., Weiler, F., Barros, F.J. and Tomaz, C. (2007) Relief of primary cervical dystonia symptoms by low frequency transcranial magnetic stimulation of the premotor cortex: case report. *Arq Neuropsiquiatr* 65: 697–699.

Allert, N., Kelm, D., Blahak, C., Capelle, H.H. and Krauss, J.K. (2010) Stuttering induced by thalamic deep brain stimulation for dystonia. *J Neural Transm* 117: 617–620.

Alterman, R.L. and Snyder, B.J. (2007) Deep brain stimulation for torsion dystonia. *Acta Neurochir Suppl* 97: 191–199.

Andrew, J., Edwards, J.M. and Rudolf Nde, M. (1974) The placement of stereotaxic lesions for involuntary movements other than in Parkinson's disease. *Acta Neurochir (Wien) Suppl* 21: 39–47.

Andrew, J., Fowler, C.J. and Harrison, M.J. (1983) Stereotaxic thalamotomy in 55 cases of dystonia. *Brain* 106: 981–1000.

Andrews, C., Viles-Olmos, I., Hariz, M. and Foltynie, T. (2010) Which patients with dystonia benefit from deep brain stimulation? A metaregression of individual patient outcomes. *J Neurol Neurosurg Psychiatry* 81: 1383–1389.

Andy, O.J. (1983) Thalamic stimulation for control of movement disorders. *Appl Neurophysiol* 46: 107–111.

Arlazoroff, A., Klein, C., Meiner, Z., Milo, R., Theitler, J. and Carpel, C.L. (1991) Tiapride as treatment for certain patients with idiopathic torsion dystonia. *Eur Neurol* 31: 356–359.

Arseni, C. and Maretsis, M. (1971) The surgical treatment of spasmodic torticollis. *Neurochirurgia (Stuttg)* 14: 177–180.

Balash, Y. and Giladi, N. (2004) Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options. *Eur J Neurol* 11: 361–370.

Bassi, S., Ferrarese, C., Frattola, L., Sbacchi, M. and Trabucchi, M. (1982) Lisuride in generalised dystonia and spasmodic torticollis. *Lancet* 1: 514–515.

Benecke, R. (2009) Xeomin in the treatment of cervical dystonia. *Eur J Neurol* 16(Suppl. 2): 6–10.

- Benecke, R. and Dressler, D. (2007) Botulinum toxin treatment of axial and cervical dystonia. *Disabil Rehabil* 29: 1769–1777.
- Benecke, R., Jost, W.H., Kanovsky, P., Ruzicka, E., Comes, G. and Grafe, S. (2005) A new botulinum toxin type a free of complexing proteins for treatment of cervical dystonia. *Neurology* 64: 1949–1951.
- Benninger, D.H., Lomarev, M., Lopez, G., Pal, N., Luckenbaugh, D.A. and Hallett, M. (2011) Transcranial direct current stimulation for the treatment of focal hand dystonia. *Mov Disord* 26: 1698–1702.
- Bertrand, C., Molina-Negro, P. and Martinez, S.N. (1978) Combined stereotactic and peripheral surgical approach for spasmodic torticollis. *Appl Neurophysiol* 41: 122–133.
- Bhidayasiri, R. and Bronstein, J.M. (2005) Improvement of cervical dystonia: possible role of transcranial magnetic stimulation simulating sensory tricks effect. *Med Hypotheses* 64: 941–945.
- Bielamowicz, S., Squirem S., Bidus, K. and Ludlow, C.L. (2001) Assessment of posterior cricoarytenoid botulinum toxin injections in patients with abductor spasmodic dysphonia. *Ann Otol Rhinol Laryngol* 110: 406–412.
- Birkent, H., Maronian, N., Waugh, P., Merati, A.L., Perkel, D. and Hillel, A.D. (2009) Dosage changes in patients with long-term botulinum toxin use for laryngeal dystonia. *Otolaryngol Head Neck Surg* 140: 43–47.
- Bittar, R.G., Yianni, J., Wang, S., Liu, X., Nandi, D., Joint, C. *et al.* (2005) Deep brain stimulation for generalised dystonia and spasmodic torticollis. *J Clin Neurosci* 12: 12–16.
- Blackie, J.D. and Lees, A.J. (1990) Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 53: 640–643.
- Blitzer, A. (2010) Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. *Eur J Neurol* 17(Suppl. 1): 28–30.
- Blitzer, A., Brin, M.F., Greene, P.E. and Fahn, S. (1989) Botulinum toxin injection for the treatment of oromandibular dystonia. *Ann Otol Rhinol Laryngol* 98: 93–97.
- Borggraefe, I., Boetzel, K., Boehmer, J., Berweck, S., Mueller-Felber, W., Mueller, K. *et al.* (2008) Return to participation - significant improvement after bilateral pallidal stimulation in rapidly progressive DYT1 dystonia. *Neuropediatrics* 39: 239–242.
- Borich, M., Arora, S. and Kimberley, T.J. (2009) Lasting effects of repeated rTMS application in focal hand dystonia. *Restor Neurol Neurosci* 27: 55–65.
- Boutsen, F., Cannito, M.P., Taylor, M. and Bender, B. (1998) Botox treatment in adductor spasmodic dysphonia: a meta-analysis. *J Speech Lang Hear Res* 45: 469–484.
- Brans, J.W., Lindeboom, R., Snoek, J.W., Zwarts, M.J., Van Weerden, T.W., Brunt, E.R. *et al.* (1996) Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 46: 1066–1072.
- Brashear, A., Lew, M.F., Dykstra, D.D., Comella, C.L., Factor, S.A., Rodnitzky, R.L. *et al.* (1999) Safety and efficacy of Neurobloc (botulinum toxin type B) in type A-responsive cervical dystonia. *Neurology* 53: 1439–1446.
- Brin, M.F., Blitzer, A. and Stewart, C. (1998) Laryngeal dystonia (spasmodic dysphonia): observations of 901 patients and treatment with botulinum toxin. *Adv Neurol* 78: 237–252.
- Brin, M.F., Comella, C.L., Jankovic, J., Lai, F. and Naumann, M. (2008) Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord* 23: 1353–1360.
- Brin, M.F., Lew, M.F., Adler, C.H., Comella, C.L., Factor, S.A., Jankovic, J. *et al.* (1999) Safety and efficacy of Neurobloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 53: 1431–1438.
- Burbaud, P., Guehl, D., Lagueny, A., Petiteau, F. and Bioulac, B. (1998) A pilot trial of clozapine in the treatment of cervical dystonia. *J Neurol* 245: 329–331.
- Burke, R.E., Fahn, S. and Marsden, C.D. (1986) Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl. *Neurology* 36: 160–164.
- Buttkus, F., Baur, V., Jabusch, H.C., Paulus, W., Nitsche, M.A. and Altenmuller, E. (2010a) Retraining and transcranial direct current stimulation in musician's dystonia - a case report. *Mov Disord* 25: 1758–1760.
- Buttkus, F., Weidenmuller, M., Schneider, S., Jabusch, H.C., Nitsche, M.A., Paulus, W. *et al.* (2010b) Failure of cathodal direct current stimulation to improve fine motor control in musician's dystonia. *Mov Disord* 25: 389–394.
- Cardoso, F., Jankovic, J., Grossman, R.G. and Hamilton, W.J. (1995) Outcome after stereotactic thalamotomy for dystonia and hemiballismus. *Neurosurgery* 36: 501–507.
- Chapman, K.L., Bartley, G.B., Waller, R.R. and Hodge, D.O. (1999) Follow-up of patients with essential blepharospasm who underwent eyelid protractor myectomy at the Mayo Clinic from 1980 through 1995. *Ophthalm Plast Reconstr Surg* 15: 106–110.

- Cho, C.B., Park, H.K., Lee, K.J. and Rha, H.K. (2009) Thalamic deep brain stimulation for writer's cramp. *J Korean Neurosurg Soc* 46: 52–55.
- Cillino, S., Raimondi, G., Guepratte, N., Damiani, S., Cillino, M., Di Pace, F. *et al.* (2010) Long-term efficacy of botulinum toxin A for treatment of blepharospasm, hemifacial spasm, and spastic entropion: a multicentre study using two drug-dose escalation indexes. *Eye (Lond)* 24: 600–607.
- Cipriani, A., Santilli, C., Furukawa, T.A., Signoretti, A., Nakagawa, A., Mcguire, H. *et al.* (2009) Escitalopram versus other antidepressive agents for depression. *Cochrane Database Syst Rev* CD006532.
- Cohen-Gadol, A.A., Ahlskog, J.E., Matsumoto, J.Y., Swenson, M.A., McClelland, R.L. and Davis, D.H. (2003) Selective peripheral denervation for the treatment of intractable spasmodic torticollis: experience with 168 patients at the Mayo Clinic. *J Neurosurg* 98: 1247–1254.
- Colbassani, H.J., Jr and Wood, J.H. (1986) Management of spasmodic torticollis. *Surg Neurol* 25: 153–158.
- Cole, R., Hallett, M., and Cohen, L.G. (1995) Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 10: 466–471.
- Comella, C.L., Jankovic, J., Truong, D.D., Hanschmann, A. and Grafe, S. (2011) Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. *J Neurol Sci* 308: 103–109.
- Comella, C.L., Shannon, K.M. and Jaglin, J. (1998) Extensor truncal dystonia: successful treatment with botulinum toxin injections. *Mov Disord* 13: 552–555.
- Contarino, M.F., Kruisdijk, J.J., Koster, L., Ongerboer, D.V., Speelman, J.D. and Koelman, J.H. (2007) Sensory integration in writer's cramp: comparison with controls and evaluation of botulinum toxin effect. *Clin Neurophysiol* 118: 2195–2206.
- Cooper, I.S. (1976) 20-year followup study of the neurosurgical treatment of dystonia musculorum deformans. *Adv Neurol* 14: 423–452.
- Costa, J., Borges, A., Espirito-Santo, C., Ferreira, J., Coelho, M., Moore, P. *et al.* (2005a) Botulinum toxin type A versus botulinum toxin type B for cervical dystonia. *Cochrane Database Syst Rev* CD004314.
- Costa, J., Espirito-Santo, C., Borges, A., Ferreira, J.J., Coelho, M., Moore, P. *et al.* (2005b) Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev* CD003633.
- Coubes, P., Cif, L., El, F.H., Hemm, S., Vayssiere, N., Serrat, S. *et al.* (2004) Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. *J Neurosurg* 101: 189–194.
- De Boer, J.E., Boomkamp, M., Broekhuijsen, F., Cheung, P.K. and Danz, M. (2012) *Farmacotherapeutisch Kompas*. Houten: Prelum Uitgevers.
- Delnooz, C.C., Horstink, M.W., Tijssen, M.A. and Van de Warrenburg, B.P. (2009) Paramedical treatment in primary dystonia: a systematic review. *Mov Disord* 24: 2187–2198.
- Diederich, N.J., Comella, C.L., Matge, G., Becker, G., Schiltz, F. and Metz, H. (1997) Sustained effect of high-dose intrathecal baclofen in primary generalized dystonia: a 2-year follow-up study. *Mov Disord* 12: 1100–1102.
- Duarte, J., Sempere, A.P., Coria, F., Claveria, L.E., Frech, F.A., Mataix, A.L. *et al.* (1995) Isolated idiopathic adult-onset foot dystonia and treatment with botulinum toxin. *J Neurol* 242: 114–115.
- Dykstra, D.D., Mendez, A., Chappuis, D., Baxter, T., Deslauriers, L. and Stuckey, M. (2005) Treatment of cervical dystonia and focal hand dystonia by high cervical continuously infused intrathecal baclofen: a report of 2 cases. *Arch Phys Med Rehabil* 86: 830–833.
- Fabinyi, G. and Dutton, J. (1980) The surgical treatment of spasmodic torticollis. *Aust N Z J Surg* 50: 155–157.
- Fahn, S., Bressman, S.B. and Marsden, C.D. (1998) Classification of dystonia. *Adv Neurol* 78: 1–10.
- Finnegan, E.M., Luschei, E.S., Gordon, J.D., Barkmeier, J.M. and Hoffman, H.T. (1999) Increased stability of airflow following botulinum toxin injection. *Laryngoscope* 109: 1300–1306.
- Foncke, E.M., Schuurman, P.R. and Speelman, J.D. (2006) Suicide after deep brain stimulation of the internal globus pallidus for dystonia. *Neurology* 66: 142–143.
- Ford, B., Greene, P.E., Louis, E.D., Bressman, S.B., Goodman, R.R., Brin, M.F. *et al.* (1998) Intrathecal baclofen in the treatment of dystonia. *Adv Neurol* 78: 199–210.
- Francis, D.A. (1983) Benzodiazepines and spasmodic torticollis. *Arch Neurol* 40: 325.
- Gauthier, S., Perot, P. and Bertrand, G. (1988) Role of surgical anterior rhizotomies in the management of spasmodic torticollis. *Adv Neurol* 50: 633–635.
- Geller, M., Kaplan, B. and Christoff, N. (1976) Treatment of dystonic symptoms with carbamazepine. *Adv Neurol* 14: 403–410.
- Georgescu, D., Vagefi, M.R., McMullan, T.F., McCann, J.D. and Anderson, R.L. (2008) Upper eyelid myectomy in blepharospasm with associated apraxia of lid opening. *Am J Ophthalmol* 145: 541–547.

- Gerretsen, P. and Pollock, B.G. (2011) Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf* 10: 751–765.
- Ghang, J.Y., Lee, M.K., Jun, S.M. and Ghang, C.G. (2010) Outcome of pallidal deep brain stimulation in Meige syndrome. *J Korean Neurosurg Soc* 48: 134–138.
- Gilbert, G.J. (1972) Haloperidol in spasmodic torticollis. *Lancet* 2: 234–235.
- Gill, H.S. and Kraft, S.P. (2010) Long-term efficacy of botulinum a toxin for blepharospasm and hemifacial spasm. *Can J Neurol Sci* 37: 631–636.
- Grassi, E., Latorraca, S., Piacentini, S., Marini, P. and Sorbi, S. (2000) Risperidone in idiopathic and symptomatic dystonia: preliminary experience. *Neurol Sci* 21: 121–123.
- Greene, P. (1992) Baclofen in the treatment of dystonia. *Clin Neuropharmacol* 15: 276–288.
- Greene, P., Shale, H. and Fahn, S. (1988a) Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. *Mov Disord* 3: 46–60.
- Greene, P., Shale, H. and Fahn, S. (1988b) Experience with high dosages of anticholinergic and other drugs in the treatment of torsion dystonia. *Adv Neurol* 50: 547–556.
- Greene, P.E. and Fahn, S. (1992) Baclofen in the treatment of idiopathic dystonia in children. *Mov Disord* 7: 48–52.
- Grivet, D., Robert, P.Y., Thuret, G., De Feligonde, O.P., Gain, P., Maugery, J. et al. (2005) Assessment of blepharospasm surgery using an improved disability scale: study of 138 patients. *Ophthal Plast Reconstr Surg* 21: 230–234.
- Gros, C., Frerebeau, P., Perez-Dominguez, E., Bazin, M. and Privat, J.M. (1976) Long term results of stereotaxic surgery for infantile dystonia and dyskinesia. *Neurochirurgia (Stuttg)* 19: 171–178.
- Gross, R.E. (2008) What happened to posteroventral pallidotomy for Parkinson's disease and dystonia? *Neurotherapeutics* 5: 281–293.
- Grosso, S., Verrotti, A., Messina, M., Sacchini, M. and Balestri, P. (2012) Management of status dystonicus in children. Cases report and review. *Eur J Paediatr Neurol*: in press
- Guettard, E., Ricard, D., Roze, E., Elbaz, A., Anheim, M., Thobois, S. et al. (2012) Risk factors for spinal cord lesions in dystonic cerebral palsy and generalised dystonia. *J Neurol Neurosurg Psychiatry* 83: 159–163.
- Hallet, M. (2011) Neurophysiology of dystonia: the role of inhibition. *Neurobiol Dis* 42: 177–184
- Hamby, W.B. and Schiffer, S. (1969) Spasmodic torticollis: results after cervical rhizotomy in 50 cases. *J Neurosurg* 31: 323–326.
- Hamby, W.B. and Schiffer, S. (1970) Spasmodic torticollis; results after cervical rhizotomy in 80 cases. *Clin Neurosurg* 17: 28–37.
- Hanagasi, H.A., Bilgic, B., Gurvit, H. and Emre, M. (2004) Clozapine treatment in oromandibular dystonia. *Clin Neuropharmacol* 27: 84–86.
- Hariz, G.M., Limousin, P., Tisch, S., Jahanshahi, M. and Fjellman-Wiklund, A. (2011) Patients' perceptions of life shift after deep brain stimulation for primary dystonia - a qualitative study. *Mov Disord* 26: 2101–2106.
- Hassler, R. and Dieckmann, G. (1970) Stereotactic treatment of different kinds of spasmodic torticollis. *Confin Neurol* 32: 135–143.
- Haussermann, P., Marczych, S., Klinger, C., Landgrebe, M., Conrad, B. and Ceballos-Baumann, A. (2004) Long-term follow-up of cervical dystonia patients treated with botulinum toxin A. *Mov Disord* 19: 303–308.
- Havrankova, P., Jech, R., Walker, N.D., Operto, G., Tauchmanova, J., Vymazal, J. et al. (2010) Repetitive TMS of the somatosensory cortex improves writer's cramp and enhances cortical activity. *Neuro Endocrinol Lett* 31: 73–86.
- Hering, S., Wenning, G.K., Seppi, K., Poewe, W. and Mueller, J. (2007) An open trial of levetiracetam for segmental and generalized dystonia. *Mov Disord* 22: 1649–1651.
- Hermanowicz, N. and Truong, D.D. (1991) Treatment of oromandibular dystonia with botulinum toxin. *Laryngoscope* 101: 1216–1218.
- Hernesniemi, J. and Keranen, T. (1990) Long-term outcome after surgery for spasmodic torticollis. *Acta Neurochir (Wien)* 103: 128–130.
- Hou, J.G., Ondo, W. and Jankovic, J. (2001) Intrathecal baclofen for dystonia. *Mov Disord* 16: 1201–1202.
- Huang, Y.Z., Rothwell, J.C., Lu, C.S., Wang, J. and Chen, R.S. (2010) Restoration of motor inhibition through an abnormal premotor-motor connection in dystonia. *Mov Disord* 25: 689–696.
- Huh, R., Han, I.B., Chung, M. and Chung, S. (2010) Comparison of treatment results between selective peripheral denervation and deep brain stimulation in patients with cervical dystonia. *Stereotact Funct Neurosurg* 88: 234–238.
- Hung, S.W., Hamani, C., Lozano, A.M., Poon, Y.Y., Piboolnurak, P., Miyasaki, J.M. et al. (2007) Long-term outcome of bilateral pallidal deep brain stimulation for primary cervical dystonia. *Neurology* 68: 457–459.
- Hwang, W.J., Calne, D.B., Tsui, J.K. and De La Fuente-Fernandez, R. (2001) The long-term response

- to levodopa in dopa-responsive dystonia. *Parkinsonism Relat Disord* 8: 1–5.
- Iacono, R.P., Kuniyoshi, S.M., Lonser, R.R., Maeda, G., Inae, A.M. and Ashwal, S. (1996) Simultaneous bilateral pallidotomy for idiopathic dystonia musculorum deformans. *Pediatr Neurol* 14: 145–148.
- Imer, M., Ozeren, B., Karadereler, S., Yapici, Z., Omay, B., Hanagasi, H. *et al.* (2005) Destructive stereotactic surgery for treatment of dystonia. *Surg Neurol* 64(Suppl. 2): S89–S94.
- Isaias, I.U., Volkmann, J., Kupsch, A., Burgunder, J.M., Ostrem, J.L., Alterman, R.L. *et al.* (2011) Factors predicting protracted improvement after pallidal DBS for primary dystonia: the role of age and disease duration. *J Neurol* 258: 1469–1476.
- Jacob, A. (1962) A case of torsion dystonia treated with orphenadrine. *Scott Med J* 7: 139–140.
- Jaffe, M.S. and Nienstedt, L.J. (2001) Intrathecal baclofen for generalized dystonia: a case report. *Arch Phys Med Rehabil* 82: 853–855.
- Jahanshahi, M., Czernecki, V. and Zurowski, A.M. (2011) Neuropsychological, neuropsychiatric, and quality of life issues in DBS for dystonia. *Mov Disord* 26(Suppl. 1): S63–S78.
- Jahanshahi, M. and Marsden, C.D. (1992) Psychological functioning before and after treatment of torticollis with botulinum toxin. *J Neurol Neurosurg Psychiatry* 55: 229–231.
- Jakobsen, J.C., Hansen, J.L., Storebo, O.J., Simonsen, E. and Gluud, C. (2011a) The effects of cognitive therapy versus ‘no intervention’ for major depressive disorder. *PLoS One* 6: e28299.
- Jakobsen, J.C., Lindschou Hansen, J., Storebo, O.J., Simonsen, E. and Gluud, C. (2011b) The effects of cognitive therapy versus ‘treatment as usual’ in patients with major depressive disorder. *PLoS One* 6: e22890.
- Jankovic, J. (1982) Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. *Ann Neurol* 11: 41–47.
- Jankovic, J. (2006) Treatment of dystonia. *Lancet Neurol* 5: 864–872.
- Jankovic, J. (2009) Clinical efficacy and tolerability of xeomin in the treatment of blepharospasm. *Eur J Neurol* 16(Suppl. 2): 14–18.
- Jankovic, J. and Beach, J. (1997) Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 48: 358–362.
- Jankovic, J. and Orman, J. (1987) Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. *Neurology* 37: 616–623.
- Jankovic, J. and Orman, J. (1988) Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology* 38: 391–394.
- Karp, B.I., Goldstein, S.R., Chen, R., Samii, A., Bara-Jimenez, W. and Hallett, M. (1999) An open trial of clozapine for dystonia. *Mov Disord* 14: 652–657.
- Katayama, Y., Fukaya, C., Kobayashi, K., Oshima, H. and Yamamoto, T. (2003) Chronic stimulation of the globus pallidus internus for control of primary generalized dystonia. *Acta Neurochir Suppl* 87: 125–128.
- Kenney, C., Hunter, C. and Jankovic, J. (2007) Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. *Mov Disord* 22: 193–197.
- Kessler, K.R., Skutta, M. and Benecke, R. (1999) Long-term treatment of cervical dystonia with botulinum toxin A: efficacy, safety, and antibody frequency. German Dystonia Study Group. *J Neurol* 246: 265–274.
- Kim, H.S., Choi, H.S., Lim, J.Y., Choi, Y.L. and Lim, S.E. (2008) Radiofrequency thyroarytenoid myotherapy for treatment of adductor spasmodic dysphonia: how we do it. *Clin Otolaryngol* 33: 621–625.
- Kiss, Z.H., Doig-Beyaert, K., Eliasziw, M., Tsui, J., Haffenden, A. and Suchowersky, O. (2007) The Canadian multicentre study of deep brain stimulation for cervical dystonia. *Brain* 130: 2879–2886.
- Kleiner-Fisman, G., Liang, G.S., Moberg, P.J., Ruocco, A.C., Hurtig, H.I., Baltuch, G.H. *et al.* (2007) Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg* 107: 29–36.
- Konrad, C., Vollmer-Haase, J., Anneken, K. and Knecht, S. (2004) Orthopedic and neurological complications of cervical dystonia - review of the literature. *Acta Neurol Scand* 109: 369–373.
- Kranz, G., Shamim, E.A., Lin, P.T., Kranz, G.S. and Hallett, M. (2010) Transcranial magnetic brain stimulation modulates blepharospasm: a randomized controlled study. *Neurology* 75: 1465–1471.
- Krauss, J.K., Loher, T.J., Pohle, T., Weber, S., Taub, E., Barlocher, C.B. *et al.* (2002) Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. *J Neurol Neurosurg Psychiatry* 72: 249–256.
- Krayenbuhl, H. and Siegfried, J. (1972) Dentatometomies or thalamotomies in the treatment of hyperkinesia. *Confin Neurol* 34: 29–33.
- Kupsch, A., Benecke, R., Muller, J., Trottenberg, T., Schneider, G.H., Poewe, W. *et al.* (2006) Pallidal



- deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med* 355: 1978–1990.
- Kuyper, D.J., Parra, V., Aerts, S., Okun, M.S. and Kluger, B.M. (2011) Nonmotor manifestations of dystonia: a systematic review. *Mov Disord* 26: 1206–1217.
- Lalli, S., Piacentini, S., Franzini, A., Panzacchi, A., Cerami, C., Messina, G. *et al.* (2012) Epidural premotor cortical stimulation in primary focal dystonia: clinical and (18) F-fluoro deoxyglucose positron emission tomography open study. *Mov Disord*, DOI: 10.1002/mds.24949.
- Lang, A.E. (1988) Dopamine agonists and antagonists in the treatment of idiopathic dystonia. *Adv Neurol* 50: 561–570.
- Langkafel, M., Heinz, A., Schols, L. and Przuntek, H. (1991) Apomorphine - test in dystonia. *J Neural Transm Park Dis Dement Sect 3*: 293–295.
- Laskawi, R. and Rohrbach, S. (2001) [Oromandibular dystonia. Clinical forms, diagnosis and examples of therapy with botulinum toxin]. *Laryngorhinootologie* 80: 708–713.
- Lew, M.F., Adornato, B.T., Duane, D.D., Dykstra, D.D., Factor, S.A., Massey, J.M. *et al.* (1997) Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. *Neurology* 49: 701–707.
- Lin, J.J. and Chang, D.C. (2004) Improvement of generalised dystonia by olanzapine treatment. *J Clin Neurosci* 11: 84–86.
- Loher, T.J., Barlocher, C.B. and Krauss, J.K. (2006) Dystonic movement disorders and spinal degenerative disease. *Stereotact Funct Neurosurg* 84: 1–11.
- Loher, T.J., Capelle, H.H., Kaelin-Lang, A., Weber, S., Weigel, R., Burgunder, J.M. *et al.* (2008) Deep brain stimulation for dystonia: outcome at long-term follow-up. *J Neurol* 255: 881–884.
- Lozano, A.M., Kumar, R., Gross, R.E., Giladi, N., Hutchison, W.D., Dostrovsky, J.O. *et al.* (1997) Globus pallidus internus pallidotomy for generalized dystonia. *Mov Disord* 12: 865–870.
- Lucetti, C., Nuti, A., Gambaccini, G., Bernardini, S., Brotini, S., Manca, M.L. *et al.* (2000) Mexiletine in the treatment of torticollis and generalized dystonia. *Clin Neuropharmacol* 23: 186–189.
- Ludlow, C.L. (2009) Treatment for spasmodic dysphonia: limitations of current approaches. *Curr Opin Otolaryngol Head Neck Surg* 17: 160–165.
- Manji, H., Howard, R.S., Miller, D.H., Hirsch, N.P., Carr, L., Bhatia, K. *et al.* (1998) Status dystonicus: the syndrome and its management. *Brain* 121: 243–252.
- Marsden, C.D., Marion, M.H. and Quinn, N. (1984) The treatment of severe dystonia in children and adults. *J Neurol Neurosurg Psychiatry* 47: 1166–1173.
- Martino, D., Macerollo, A., Abbruzzese, G., Bentivoglio, A.R., Berardelli, A., Esposito, M. *et al.* (2010) Lower limb involvement in adult-onset primary dystonia: frequency and clinical features. *Eur J Neurol* 17: 242–246.
- Messina, G., Cordella, R., Dones, I., Tringali, G. and Franzini, A. (2011) Improvement of a secondary fixed dystonia of the upper limb after chronic extradural motor cortex stimulation in 10 patients: first reported series. *Neurosurgery*, in press.
- Mezaki, T., Kaji, R., Hamano, T., Nagamine, T., Shibasaki, H., Shimizu, T. *et al.* (1994) Optimisation of botulinum treatment for cervical and axial dystonias: experience with a Japanese type A toxin. *J Neurol Neurosurg Psychiatry* 57: 1535–1537.
- Moll, C.K., Hamel, W., Ostertag, C.B., Muller, D., Finsterbusch, J., Engel, A.K. *et al.* (2008) Subthalamotomy in cervical dystonia: a case study of lesion location and clinical outcome. *Mov Disord* 23: 1751–1756.
- Munchau, A., Palmer, J.D., Dressler, D., O'Sullivan, J.D., Tsang, K.L., Jahanshahi, M. *et al.* (2001) Prospective study of selective peripheral denervation for botulinum-toxin resistant patients with cervical dystonia. *Brain* 124: 769–783.
- Munding, F. (1977) [New stereotactic treatment of spasmodic torticollis with a brain stimulation system]. *Med Klin* 72: 1982–1986.
- Munding, F., Riechert, T. and Disselhoff, J. (1972) Long-term results of stereotactic treatment of spasmodic torticollis. *Confin Neurol* 34: 41–50.
- Murase, N., Rothwell, J.C., Kaji, R., Urushihara, R., Nakamura, K., Murayama, N. *et al.* (2005) Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain* 128: 104–115.
- Nakamura, K., Muta, H., Watanabe, Y., Mochizuki, R., Yoshida, T. and Suzuki, M. (2008) Surgical treatment for adductor spasmodic dysphonia - efficacy of bilateral thyroarytenoid myectomy under microlaryngoscopy. *Acta Otolaryngol* 128: 1348–1353.
- Newman, R.P., Lewitt, P.A., Shults, C., Bruno, G., Foster, N.L., Chase, T.N. *et al.* (1985) Dystonia: treatment with bromocriptine. *Clin Neuropharmacol* 8: 328–333.
- Nicoletti, A.G., Pereira, I.C. and Matayoshi, S. (2009) Browlifting as an alternative procedure for apraxia of eyelid opening. *Ophthal Plast Reconstr Surg* 25: 46–47.

- Nutt, J.G. and Nygaard, T.G. (2001) Response to levodopa treatment in dopa-responsive dystonia. *Arch Neurol* 58: 905–910.
- Ochudlo, S., Bryniarski, P. and Opala, G. (2007) Botulinum toxin improves the quality of life and reduces the intensification of depressive symptoms in patients with blepharospasm. *Parkinsonism Relat Disord* 13: 505–508.
- Odergren, T., Hjaltason, H., Kaakkola, S., Solders, G., Hanko, J., Fehling, C. *et al.* (1998) A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* 64: 6–12.
- Ohara, S., Hayashi, R., Momoi, H., Miki, J. and Yanagisawa, N. (1998) Mexiletine in the treatment of spasmodic torticollis. *Mov Disord* 13: 934–940.
- Olver, J., Esquenazi, A., Fung, V.S., Singer, B.J. and Ward, A.B. (2010) Botulinum toxin assessment, intervention and aftercare for lower limb disorders of movement and muscle tone in adults: international consensus statement. *Eur J Neurol* 17(Suppl. 2): 57–73.
- Ondo, W.G., Desaloms, J.M., Jankovic, J. and Grossman, R.G. (1998) Pallidotomy for generalized dystonia. *Mov Disord* 13: 693–698.
- Ostrem, J.L., Marks, W.J., Jr, Volz, M.M., Heath, S.L. and Starr, P.A. (2007) Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome). *Mov Disord* 22: 1885–1891.
- Ostrem, J.L., Racine, C.A., Glass, G.A., Grace, J.K., Volz, M.M., Heath, S.L. *et al.* (2011) Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology* 76: 870–878.
- Pahapill, P.A. and O’Connell, B. (2010) Long-term follow-up study of chronic deep brain stimulation of the subthalamic nucleus for cervical dystonia. *Neuromodulation* 13: 26–30.
- Pappert, E.J. and Germanson, T. (2008) Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: randomized, double-blind, noninferiority trial. *Mov Disord* 23: 510–517.
- Patil, B. and Foss, A.J. (2009) Upper lid orbicularis oculi muscle strip and sequential brow suspension with autologous fascia lata is beneficial for selected patients with essential blepharospasm. *Eye (Lond)* 23: 1549–1553.
- Pont-Sunyer, C., Marti, M.J. and Tolosa, E. (2010) Focal limb dystonia. *Eur J Neurol* 17(Suppl. 1): 22–27.
- Poungvarin, N., Devahastin, V., Chaisevikul, R., Prayoonwiwat, N. and Viriyavejakul, A. (1997) Botulinum A toxin treatment for blepharospasm and Meige syndrome: report of 100 patients. *J Med Assoc Thai* 80: 1–8.
- Quartarone, A., Rizzo, V. and Morgante, F. (2008) Clinical features of dystonia: a pathophysiological revisit. *Curr Opin Neurol* 21: 484–490.
- Quinn, N.P., Lang, A.E., Sheehy, M.P. and Marsden, C.D. (1985) Lisuride in dystonia. *Neurology* 35: 766–769.
- Racette, B.A., Lauryssen, C. and Perlmutter, J.S. (1998) Preoperative treatment with botulinum toxin to facilitate cervical fusion in dystonic cerebral palsy. Report of two cases. *J Neurosurg* 88: 328–330.
- Ranoux, D., Gury, C., Fondarai, J., Mas, J.L. and Zuber, M. (2002) Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry* 72: 459–462.
- Reese, R., Gruber, D., Schoenecker, T., Bazner, H., Blahak, C., Capelle, H.H. *et al.* (2011) Long-term clinical outcome in Meige syndrome treated with internal pallidum deep brain stimulation. *Mov Disord* 26: 691–698.
- Remacle, M., Plouin-Gaudon, I., Lawson, G. and Abitbol, J. (2005) Bipolar radiofrequency-induced thermotherapy (RFITT) for the treatment of spasmodic dysphonia. A report of three cases. *Eur Arch Otorhinolaryngol* 262: 871–874.
- Roggenkamper, P., Jost, W.H., Bihari, K., Comes, G. and Grafe, S. (2006) Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm* 113: 303–312.
- Romito, L.M., Franzini, A., Perani, D., Carella, F., Marras, C., Capus, L. *et al.* (2007) Fixed dystonia unresponsive to pallidal stimulation improved by motor cortex stimulation. *Neurology* 68: 875–876.
- Schneider, S.A., Edwards, M.J., Grill, S.E., Goldstein, S., Kanchana, S., Quinn, N.P. *et al.* (2006a) Adult-onset primary lower limb dystonia. *Mov Disord* 21: 767–771.
- Schneider, S.A., Mohire, M.D., Trender-Gerhard, I., Asmus, F., Sweeney, M., Davis, M. *et al.* (2006b) Familial dopa-responsive cervical dystonia. *Neurology* 66: 599–601.
- Siebner, H.R., Auer, C., Ceballos-Baumann, A. and Conrad, B. (1999a) Has repetitive transcranial magnetic stimulation of the primary motor hand area a therapeutic application in writer’s cramp? *Electroencephalogr Clin Neurophysiol Suppl* 51: 265–275.
- Siebner, H.R., Tormos, J.M., Ceballos-Baumann, A.O., Auer, C., Catala, M.D., Conrad, B. *et al.* (1999b) Low-frequency repetitive transcranial

- magnetic stimulation of the motor cortex in writer's cramp. *Neurology* 52: 529–537.
- Singer, B. J., Dunne, J. W., Singer, K. P., Jegasothy, G.M. and Allison, G.T. (2004) Non-surgical management of ankle contracture following acquired brain injury. *Disabil Rehabil* 26: 335–345.
- Singer, C. and Papapetropoulos, S. (2006) Adult-onset primary focal foot dystonia. *Parkinsonism Relat Disord* 12: 57–60.
- Slawek, J., Friedman, A., Potulska, A., Krystkowiak, P., Gervais, C., Banach, M. *et al.* (2007) Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* 22: 95–100.
- Speelman, J.D., Van Manen, J., Jacz, K. and Van Beusekom, G.T. (1987) The Foerster–Dandy operation for the treatment of spasmodic torticollis. *Acta Neurochir Suppl (Wien)* 39: 85–87.
- Stahl, S.M. and Berger, P.A. (1981) Bromocriptine in dystonia. *Lancet* 2: 745.
- Stamelou, M., Edwards, M.J., Hallett, M. and Bhatia, K.P. (2011) The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain*, DOI: 10.1093/brain/awr224.
- Steinberger, D., Korinthenberg, R., Topka, H., Berghauer, M., Wedde, R. and Muller, U. (2000) Dopa-responsive dystonia: mutation analysis of GCH1 and analysis of therapeutic doses of L-dopa. German Dystonia Study Group. *Neurology* 55: 1735–1737.
- Strang, R.R. (1967) A comparative study of chlorzoxazone, phenylamidol and hydramitrazine in the treatment of spasmodic torticollis. *Curr Med Drugs* 8: 19–31.
- Sullivan, K.L., Hauser, R.A., Louis, E.D., Chari, G. and Zesiewicz, T.A. (2005) Levitracetam for the treatment of generalized dystonia. *Parkinsonism Relat Disord* 11: 469–471.
- Tagliati, M., Krack, P., Volkmann, J., Aziz, T., Krauss, J.K., Kupsch, A. *et al.* (2011) Long-term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. *Mov Disord* 26(Suppl. 1): S54–S62.
- Taira, T. and Hori, T. (2003a) A novel denervation procedure for idiopathic cervical dystonia. *Stereotact Funct Neurosurg* 80: 92–95.
- Taira, T. and Hori, T. (2003b) Stereotactic ventrooralis thalamotomy for task-specific focal hand dystonia (writer's cramp). *Stereotact Funct Neurosurg* 80: 88–91.
- Tan, E.K. and Jankovic, J. (1999) Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. *Neurology* 53: 2102–2107.
- Tasker, R.R., Doorly, T. and Yamashiro, K. (1988) Thalamotomy in generalized dystonia. *Adv Neurol* 50: 615–631.
- Teive, H.A., Munhoz, R.P., Souza, M.M., Antoniuk, S.A., Santos, M.L., Teixeira, M.J. *et al.* (2005) Status dystonicus: study of five cases. *Arq Neuropsiquiatr* 63: 26–29.
- Ten Houten, R., Lakke, J.P., De Jong, P., Van Weerden, T.W., Van Den Burg, W., and Wesseling, H. (1984) Spasmodic torticollis: treatment with tizanidine. *Acta Neurol Scand* 70: 373–376.
- Thiel, A., Dressler, D., Kistel, C. and Ruther, E. (1994) Clozapine treatment of spasmodic torticollis. *Neurology* 44: 957–958.
- Tonomura, Y., Kataoka, H., Sugie, K., Hirabayashi, H., Nakase, H. and Ueno, S. (2007) Atlantoaxial rotatory subluxation associated with cervical dystonia. *Spine (Phila Pa 1976)* 32: E561–E564.
- Traynelis, V.C., Ryken, T., Rodnitzky, R.L. and Menezes, A.H. (1992) Botulinum toxin enhancement of postoperative immobilization in patients with cervical dystonia. Technical note. *J Neurosurg* 77: 808–809.
- Truong, D.D., Rontal, M., Rolnick, M., Aronson, A.E. and Mistura, K. (1991) Double-blind controlled study of botulinum toxin in adductor spasmodic dysphonia. *Laryngoscope* 101: 630–634.
- Truong, D.D., Sandroni, P., Van Den Noort, S. and Matsumoto, R.R. (1995) Diphenhydramine is effective in the treatment of idiopathic dystonia. *Arch Neurol* 52: 405–407.
- Truong, D.D., Comella, C., Fernandez, H.H. and Ondo, W.G. (2008) Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: a randomized placebo-controlled phase II trial. *Park Rel Dis* 14: 407–414.
- Truong, D.D., Duane, D.D., Jankovic, J., Singer, C., Seeberger, L.C., Comella, C.L., *et al.* (2005) Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. *Mov Disord* 20: 783–791.
- Tsui, J.K., Bhatt, M., Calne, S. and Calne, D.B. (1993) Botulinum toxin in the treatment of writer's cramp: a double-blind study. *Neurology* 43: 183–185.
- Tsuji, D.H., Chrispim, F.S., Imamura, R., Sennes, L.U. and Hachiya, A. (2006) Impact in vocal quality in partial myectomy and neurectomy endoscopic of thyroarytenoid muscle in patients with adductor

- spasmodic dysphonia. *Braz J Otorhinolaryngol* 72: 261–266.
- Valledeoriola, F., Regidor, I., Mínguez-Castellanos, A., Lezcano, E., Garcia-Ruiz, P., Rojo, A. *et al.* (2010) Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish multicentric study. *J Neurol Neurosurg Psychiatry* 81: 65–69.
- Van den Bergh, P., Francart, J., Mourin, S., Kollmann, P. and Laterre, E.C. (1995) Five-year experience in the treatment of focal movement disorders with low-dose Dysport botulinum toxin. *Muscle Nerve* 18: 720–729.
- Vasques, X., Cif, L., Gonzalez, V., Nicholson, C. and Coubes, P. (2009) Factors predicting improvement in primary generalized dystonia treated by pallidal deep brain stimulation. *Mov Disord* 24: 846–853.
- Vercueil, L., Pollak, P., Fraix, V., Caputo, E., Moro, E., Benazzouz, A. *et al.* (2001) Deep brain stimulation in the treatment of severe dystonia. *J Neurol* 248: 695–700.
- Vidailhet, M., Vercueil, L., Houeto, J.L., Krystkowiak, P., Benabid, A.L., Cornu, P. *et al.* (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med* 352: 459–467.
- Vidailhet, M., Vercueil, L., Houeto, J.L., Krystkowiak, P., Lagrange, C., Yelnik, J. *et al.* (2007) Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol* 6: 223–229.
- Wabbels, B., Reichel, G., Fulford-Smith, A., Wright, N. and Roggenkamper, P. (2011) Double-blind, randomised, parallel group pilot study comparing two botulinum toxin type A products for the treatment of blepharospasm. *J Neural Transm* 118: 233–239.
- Wabbels, B. and Roggenkamper, P. (2007) Long-term follow-up of patients with frontalis sling operation in the treatment of essential blepharospasm unresponsive to botulinum toxin therapy. *Graefes Arch Clin Exp Ophthalmol* 245: 45–50.
- Walker, R.H., Danisi, F.O., Swope, D.M., Goodman, R.R., Germano, I.M. and Brin, M.F. (2000) Intrathecal baclofen for dystonia: benefits and complications during six years of experience. *Mov Disord* 15: 1242–1247.
- Watts, C., Nye, C. and Whurr, R. (2006) Botulinum toxin for treating spasmodic dysphonia (laryngeal dystonia): a systematic Cochrane review. *Clin Rehabil* 20: 112–122.
- Watts, C.R., Truong, D.D. and Nye, C. (2008) Evidence for the effectiveness of botulinum toxin for spasmodic dysphonia from high-quality research designs. *J Neural Transm* 115: 625–630.
- West, H.H. (1977) Treatment with amantadine in spasmodic torticollis: a double blind study. *Neurology* 27: 198–199.
- Whurr, R., Nye, C. and Lorch, M. (1998) Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. *Int J Lang Commun Disord* 33: 327–329.
- Wohrle, J.C., Weigel, R., Grips, E., Blahak, C., Capelle, H.H. and Krauss, J.K. (2003) Risperidone-responsive segmental dystonia and pallidal deep brain stimulation. *Neurology* 61: 546–548.
- Wong, A.S., Massicotte, E.M. and Fehlings, M.G. (2005) Surgical treatment of cervical myeloradiculopathy associated with movement disorders: indications, technique, and clinical outcome. *J Spinal Disord Tech* 18(Suppl.): S107–S114.
- Wong, D.L., Adams, S.G., Irish, J.C., Durkin, L.C., Hunt, E.J. and Charlton, M.P. (1995) Effect of neuromuscular activity on the response to botulinum toxin injections in spasmodic dysphonia. *J Otolaryngol* 24: 209–216.
- Woodson, G., Hochstetler, H. and Murry, T. (2006) Botulinum toxin therapy for abductor spasmodic dysphonia. *J Voice* 20: 137–143.
- Yardimci, N., Karatas, M., Kilinc, M. and Benli, S. (2006) Levetiracetam in Meige's syndrome. *Acta Neurol Scand* 114: 63–66.
- Yoshimura, D.M., Aminoff, M.J. and Olney, R.K. (1992) Botulinum toxin therapy for limb dystonias. *Neurology* 42: 627–630.
- Yoshor, D., Hamilton, W.J., Ondo, W., Jankovic, J. and Grossman, R.G. (2001) Comparison of thalamotomy and pallidotomy for the treatment of dystonia. *Neurosurgery* 48: 818–824.
- Zesiewicz, T.A., Louis, E.D., Sullivan, K.L., Menkin, M., Dunne, P.B. and Hauser, R.A. (2004) Substantial improvement in a Meige's syndrome patient with levetiracetam treatment. *Mov Disord* 19: 1518–1521.
- Ziegler, D.K. (1981) Prolonged relief of dystonic movements with diazepam. *Neurology* 31: 1457–1458.
- Zuddas, A. and Cianchetti, C. (1996) Efficacy of risperidone in idiopathic segmental dystonia. *Lancet* 347: 127–128.