Cervical dystonia, also referred to as spasmodic torticollis, is the most frequent form of adult-onset focal dystonia seen in neurological practice. It is characterized by involuntary contractions in a specific set of muscles causing abnormal, sustained and frequently painful postures of the head, neck and shoulders. Intramuscular injection of botulinum toxin (BoNT) into selected muscles is currently considered the treatment of first choice. This has been confirmed by numerous short- and long-term clinical studies, which have established high-quality class I and II evidence (level A recommendation by the American Academy of Neurology) that both BoNT-A and BoNT-B are safe and effective treatment options for cervical dystonia. This review summarizes the clinical evidence currently available and attempts to provide an overview of ongoing clinical studies in this field.

Keywords: antibody • botulinum toxin type A • botulinum toxin type B • dystonia • secondary nonresponsiveness • spasmodic torticollis

Dystonia is a heterogeneous group of movement disorders characterized by involuntary sustained contractions of both agonist and antagonist muscles, frequently causing repetitive twisting movements or abnormal postures, which can affect any body region (reviewed in [1,2]). Although originally considered rare, recent epidemiological studies have suggested that the disease is frequently under- or mis-diagnosed and sporadic ‘idiopathic’ focal dystonia is now considered the third most common movement disorder [3–6]. Idiopathic cervical dystonia (CD), also referred to as spasmodic torticollis, is the most frequent form of focal dystonia seen in neurological practice and causes abnormal postures of the head, neck and shoulders, due to overactivity of neck and shoulder muscles, sometimes superimposed by tremulous and/or myoclonic movements. Age of onset is typically approximately 40 years, with wide variability. The incidence is estimated as 6 and 9/100,000 in the USA [7] and central Europe [4], respectively, although the prevalence in the general community may be considerably higher based on the few epidemiological community-based studies currently available [3]. One study in a multiethnic population in northern California suggested the minimum incidence to be higher in white individuals compared with other races, for example, Hispanic, Asian and Afro-Caribbean [8]. Women are affected between 1.5- and 1.9-times more frequently than men. Symptoms of CD may vary from mild to severe, are frequently painful, may lead to disability by interference with activities of daily living, such as driving, working and reading, and frequently result in social withdrawal. Spontaneous remission may occur in approximately 10–20% of patients [9], but in most of these patients symptoms later reappear, often resulting in permanent disability. The majority of patients report relief from sensory tricks (‘geste antagoniste’), such as lightly touching the chin or leaning the head back against support; in a few patients, ‘reverse’ sensory tricks have been reported [10].
The phenomology of CD is complex, with variable combinations of tonic (sustained) and phasic (intermittent) movements. Depending on the predominant plane of movement, involuntary head movements are termed torticollis (rotation of the head on a transversal plane), antecollis/retrocollis (flexion/extension of the head on a sagittal plane) or laterocollis (flexion of the head on a frontal plane). Most patients suffer from a combination of these components of movement.

Although it is commonly thought that abnormal neuronal activities, most likely within the basal ganglia motor loops, underlie dystonic symptoms, the detailed pathogenesis of CD is still largely mysterious. Various studies revealed a high proportion of patients with a positive family history (<25%) [11,12], suggesting a hereditary component in the pathogenesis in at least a considerable subset of patients. Segregation analysis suggested that focal dystonia may be inherited as an autosomal dominant trait, with a reduced penetrance of approximately 12–15% [12–14]. In line with these findings, several recent genetic studies found an association of single nucleotide polymorphisms within or in close proximity to the TOR1A(DYT1) and TOR1B-genes on chromosome 9p, with sporadic focal dystonia in independent populations [15–17]. However, these results need to be confirmed in further populations, especially because one study in German patients with controls failed to obtain similar results [18].

The fact that findings from recent neurophysiological and imaging studies have revealed several abnormalities shared by different types of focal dystonia, including CD, supports the hypothesis that these clinically diverse subtypes of dystonia may have common etiological factors, including genetic susceptibility. Taken together, these shared pathological findings point to abnormalities in sensorimotor integration and cortical excitability, with loss of surround inhibition mediated by GABA and aberrant or maladaptive plasticity of specific brain regions as major common themes. These appear to be due to, among other factors, abnormal levels of activity in the sensorimotor cortex, the caudal sensorimotor area and premotor cortices during motor tasks, volumetric enlargement of the basal ganglia, altered dopamine D2-receptor binding and an increase in grey matter density in the primary sensory cortex (reviewed in [19–21]). Diffusion tensor imaging studies are one example where neuroimaging studies have exhibited discordance between different subtypes of focal dystonia. These studies have demonstrated ultrastructural white matter changes in the corpus callosum, prefrontal cortex, sensorimotor area, caudate, putamen and thalamus in patients with CD [22,23], whereas no such changes were observed in those with blepharospasm [24]. Secondary dystonia may be caused by exposure to neuroleptic drugs blocking dopamine receptors, stroke, various neurodegenerative conditions, post-traumatic dystonia, perinatal brain injury, infections or other causes.

Intramuscular injection of botulinum toxin (BoNT) into selected muscles is currently considered the treatment of first choice for CD. If necessary, this therapy may be combined with pharmacological and/or neurosurgical treatment options. Oral medications to be considered include anticholinergics such as trihexyphenidyl, muscle relaxants such as baclofen and benzodiazepines, or antiparkinsonian drugs such as tetrabenazine. However, side effects including dry mouth, dizziness or sedation frequently outweigh the therapeutic benefits [25], and evidence from controlled trials is either completely lacking or poor. Pallidal deep-brain stimulation of the globus pallidus internus may also be considered for selected patients if BoNT injections and medication have failed to provide sufficient relief, especially for complex cervical or segmental dystonia [26,27]. Recently, preliminary results from a small prospective pilot study on the effects of bilateral deep-brain stimulation of the subthalamic nucleus in nine patients with predominant CD also suggested a significant improvement, with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score improving from a mean (± standard error of the mean) of 53.1 (± 2.57) to 19.6 (± 5.48) at 12 months (p < 0.001). No bradykinetic side effects were observed, but transient dyskinesias during stimulation occurred in all patients and transient worsening of depression and weight gain in some [28]. Peripheral surgical procedures that may be considered in selected cases refractory to other types of treatment include selective peripheral denervation and myectomy [29].

Serotypes of BoNT & commercially available preparations

Botulinum toxin is produced by the bacterium Clostridium botulinum. Seven distinct immunological serotypes can be differentiated, classified into A–G [30]. Their biological activity is largely determined by which protein components of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-complex they interact with. These proteins are required for membrane fusion preceding release of acetylcholine-containing vesicles into the synaptic cleft at the neuromuscular junction. The BoNT light chain acts as a protease and catalyzes zinc-dependent cleavage at specific sites of one or more of these SNARE proteins, depending on the BoNT serotype (e.g., BoNT-A, BoNT-E: SNAP-25 and BoNT-B: VAMP/synaptobrevin). All commercially available
BoNT preparations currently available are either based upon BoNT-A, such as Botox® (onabotulinumtoxinA; Allergan Inc., CA, USA), Dysport® (abobotulinumtoxinA; Ipsen Ltd, Slough, UK), and Xeomin® (incobotulinumtoxinA; Merz Pharmaceuticals, Frankfurt, Germany) or upon BoNT-B, such as MyoblocTM (as marketed in the USA; rimabotulinumtoxinB; Solstice Neurosciences Inc., PA, USA) and Neurobloc® (as marketed elsewhere; rimabotulinumtoxinB; Solstice Neurosciences Inc.). In Japan, serotype F has previously also been available on a limited basis [31], but its short duration of benefit appears to be a major disadvantage in clinical practice. These BoNT drugs differ in their protein composition, strength and amounts, as well as their commercial processing. According to currently available data, it is thought that Botox and Xeomin are highly similar with respect to their therapeutic effects and profile of side effects in clinical practice [32–34]. Their biological activity or potency, as measured in mouse units per vial, appears to be comparable in clinical routine and in clinical studies [32,35], although the potency units for each brand are specific for the preparation and assay method utilized. In contrast, the dose conversion ratio of Botox versus Dysport has remained a matter of debate; some currently available studies [36,37] suggest a conversion ratio in the order of 1:3–1:4, although these two studies, directly comparing one brand (Botox) to another (Dysport) in an effort to establish a dose equivalency, showed that there was considerable interindividual variability. Whereas the authors of the first study inferred from their data that the dose equivalency of Botox to Dysport was 1:3 [36], the second study, using a three-period crossover design, concluded that this ratio is less than 1:3 [37]. A third study, termed Retrospective Evaluation of the Dose of Dysport and Botox in the Clinical Management of Cervical Dystonia and Blepharospasm (‘REAL DOSE’), which was retrospective and also included patients with blepharospasm, found a wide range of Dysport:Botox ratios, ranging from a low of 2:1 to a high of 11:1; only 21% of all patients (n = 116) fell into the ratio grouping of 3:1 to less than 4:1, therefore questioning the results of the two other previous studies mentioned above and suggesting that clinical decisions regarding the dosage of different BoNT formulations has to be made on an individual basis for each patient [38]. The conversion ratio between Botox and Myobloc/Neurobloc is presumed to lie in the order of 1:40–1:50. In clinical practice, the treating physician must be aware that each brand is unique and that simple dose-conversion ratios are not applicable; therefore, caution should be used, especially when it is necessary to switch between different brands in a given patient. Varying dilutions may further complicate attempts to compare the dosage of different BoNT formulations due to their effects on potency, clinical efficacy and frequency of possible adverse events. Xeomin is a relatively new formulation of BoNT-A containing only the active neurotoxin without accessory (complexing) proteins. Based on its pharmacological properties, it is assumed that its antigenicity and the resulting risk of developing neutralizing antibodies (nAbs) against BoNT may be lower when compared with other available types of BoNT-A. One double-blind non-inferiority study has established similar clinical effects and safety compared with Botox in CD patients [32]. The actual frequency of development of nAb still remains to be determined, although preliminary results are encouraging: an open-label study of 100 patients with CD (50 de novo, 50 previously treated with BoNT) continuously treated with Xeomin over 2 years showed negative antibody test results in all patients, using the sensitive mouse hemidiaphragma assay [39]. However, the abovementioned hypothesis further awaits testing in larger and long-term clinical studies. A recent meta-analysis of 70 published studies indicated some differences in adverse events profiles between BoNT formulations, with a higher rate of dysphagia associated with Dysport and a higher frequency of dry mouth associated with Myobloc treatment [40]. Nevertheless, in summary, there is so far no evidence unequivocally demonstrating superiority of one formulation of BoNT-A over the others.

Clinical studies with BoNT-A in CD

Off-label treatment of CD patients with BoNT-A was pioneered in the mid to late 1980s by Tsui and colleagues (among others), who published the first single-blind pilot study of 12 CD patients [41]. This was followed 1 year later by the first double-blind study in 21 patients [42]. Over the following years, approximately 80 clinical studies have been published that evaluate BoNT as treatment for CD, most of them short-term studies, but more recently also including some long-term observations with up to 12 years of follow-up. Of these, 14 can be classified as controlled clinical trials, including seven prospective, double-blind, randomized studies meeting the criteria for classification as class I evidence, four with BoNT-A and three with BoNT-B. Taken together, the results clearly demonstrate that BoNT, in properly adjusted doses, is an effective and safe treatment of CD, which has led to the official recommendation by the American Academy of Neurology that “BoNT injection should be offered as a treatment option to patients with CD (level A) and is probably more efficacious and better tolerated in patients with CD than trihexyphenidyl.
Clinical trials with BoNT-B in CD

Since BoNT are bacterial proteins, one major problem associated with BoNT treatment of CD is the potential of these proteins to elicit an immunologic response when injected into humans, with development of nAbs against the neurotoxin and/or accessory proteins and subsequent clinical secondary nonresponsiveness. If this occurs, those patients who require long-term symptomatic treatment are permanently deprived of their first-line treatment option. It should be mentioned, however, that measurement of nAbs is technically demanding and that some patients with nAbs, as measured in the mouse protection assay, may clinically still respond to BoNT injections. Although the precise individual risk for development of nAbs in a given patient is difficult to determine, potential risk factors include the dose of BoNT used per treatment cycle, the interval between injections and the formulation of BoNT, including its total protein load and specific biological activity [44,45,47]. Accordingly, the introduction of a new serotype of BoNT into clinical practice, BoNT-B, with its differing pharmacological properties, raised hopes that it may represent an alternative treatment option for such CD patients who have developed nAbs against BoNT-A. So far, six controlled, multicenter, double-blind studies evaluating the safety and efficacy of BoNT-B have been published, three of them placebo-controlled [48-50] and three of them directly comparing BoNT-A with BoNT-B [51-53]. In the placebo-controlled studies, TWSTRS scores improved significantly following BoNT-B treatment. The comparative studies showed that clinical improvement of CD at 4 weeks after treatment with BoNT-B was comparable to that after BoNT-A treatment, but autonomic side effects, especially dry mouth and dysphagia [51], and, in one study also constipation [52], were significantly more frequent with BoNT-B, although these side effects were mostly mild and not disabling, and the frequency of dry mouth appeared to decrease with subsequent injections [54]. The duration of effect was slightly shorter with BoNT-B [51]. This disadvantageous profile of side effects was confirmed in further smaller studies [40,55,56]. In addition, several studies or case series suggest a higher antigenicity of BoNT-B and therefore higher risk of developing nAbs compared with BoNT-A. In two small case series, five of nine patients (44%) and six of ten patients developed nAbs over time [57,58]. In a larger cohort, dosage had to be increased linearly over time, but nevertheless the clinical benefit was clearly diminished [54]. In another large series of 100 patients followed over an average of 1.5 years, 30% developed nAbs [59]. By contrast, the risk of nAb formation associated with BoNT-A treatment appeared to be low, approximately 1.2% with Botox (new formulation with lower protein load) [45,60] and approximately between 0 and 3% with Dysport, although these latter studies had some technical limitations [46,61,62]. Based on these findings, most experts currently suggest that BoNT-A should generally be considered the front-line treatment for CD, and that BoNT-B, although it has US FDA indication for CD in the USA, should primarily be considered as an option for patients who have developed nAbs against BoNT-A (e.g., [63,64]). Other experts, however, argue that due to methodological constraints, caution should be used in interpreting the abovementioned studies and that BoNT-B can also be used as initial treatment for CD [53].

Ongoing clinical studies

Various clinical trials further evaluating the efficacy and safety of different formulations of BoNT in patients with CD are currently underway (actively recruiting), whereas others have been completed but results have not yet been published. By examining [101], the central registry of federally and privately supported clinical trials conducted in the USA and around the world, four such studies are listed as actively recruiting. One prospective case-control study evaluating the effects of BoNT treatment on afferent sensory input using magnetoencephalography (NCT01056861); one prospective observational trial (Cervical Dystonia Patient Registry for the Observation of Botulinum Toxin Type A Efficacy [CD-PROBE, NCT00836017]); one randomized, double-blind study comparing the efficacy and safety of Botox versus Dysport in moderate to severe CD (NCT00528541);
Table 1. Clinical studies assessing the effects of botulinum toxin treatment in patients with cervical dystonia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Class</th>
<th>Number of patients</th>
<th>Max. dose (units)</th>
<th>Responder (%) dystonia</th>
<th>Responder (%) pain</th>
<th>Scale</th>
<th>Improvement (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Botox® (BoNT-A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsui et al. (1986)</td>
<td>Double-blind</td>
<td>II</td>
<td>21</td>
<td>100</td>
<td>63</td>
<td>89</td>
<td>Tsui</td>
<td>30</td>
<td>[42]</td>
</tr>
<tr>
<td>Gelb et al. (1989)</td>
<td>Double-blind</td>
<td>II</td>
<td>20</td>
<td>280</td>
<td>15</td>
<td>50</td>
<td>Tsui</td>
<td>20</td>
<td>[68]</td>
</tr>
<tr>
<td>Gelb et al. (1991)</td>
<td>Double-blind</td>
<td>III</td>
<td>28</td>
<td>280</td>
<td>32</td>
<td>64</td>
<td>Tsui</td>
<td>20</td>
<td>[69]</td>
</tr>
<tr>
<td>Greene et al. (1990)</td>
<td>Double-blind</td>
<td>I</td>
<td>55</td>
<td>240</td>
<td>74</td>
<td>N/A</td>
<td>GIR (0–3)</td>
<td>33</td>
<td>[70]</td>
</tr>
<tr>
<td>Jankovic &amp; Schwartz (1990)</td>
<td>Open-label</td>
<td>III</td>
<td>195</td>
<td>209</td>
<td>90</td>
<td>93</td>
<td>GIR (0–4)</td>
<td>&gt;50</td>
<td>[71]</td>
</tr>
<tr>
<td>Koller et al. (1990)*</td>
<td>Double-blind</td>
<td>II</td>
<td>30</td>
<td>150</td>
<td>52</td>
<td>N/A</td>
<td>GIR (0–3)</td>
<td>N/S</td>
<td>[72]</td>
</tr>
<tr>
<td>Lorentz et al. (1991)</td>
<td>Double-blind</td>
<td>II</td>
<td>23</td>
<td>150</td>
<td>87</td>
<td>63</td>
<td>Tsui</td>
<td>33</td>
<td>[73]</td>
</tr>
<tr>
<td>Comella et al. (1992)</td>
<td>Open-label</td>
<td>III</td>
<td>52</td>
<td>374</td>
<td>71</td>
<td>86</td>
<td>TWSTRS</td>
<td>&gt;10</td>
<td>[67]</td>
</tr>
<tr>
<td>Naumann et al. (2002)*</td>
<td>Open-label</td>
<td>III</td>
<td>133</td>
<td>155</td>
<td>100*</td>
<td>100*</td>
<td>TWSTRS</td>
<td>&gt;10</td>
<td>[74]</td>
</tr>
<tr>
<td><strong>Dysport® (BoNT-A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blackie et al. (1990)</td>
<td>Double-blind</td>
<td>II</td>
<td>19</td>
<td>960</td>
<td>84</td>
<td>75</td>
<td>Tsui</td>
<td>22</td>
<td>[75]</td>
</tr>
<tr>
<td>Stell et al. (1989)</td>
<td>Open-label</td>
<td>III</td>
<td>10</td>
<td>1200</td>
<td>90</td>
<td>100</td>
<td>Tsui</td>
<td>47</td>
<td>[76]</td>
</tr>
<tr>
<td>Poeve et al. (1992)</td>
<td>Open-label</td>
<td>III</td>
<td>37</td>
<td>632</td>
<td>86</td>
<td>84</td>
<td>Tsui</td>
<td>&gt;50</td>
<td>[77]</td>
</tr>
<tr>
<td>Brans et al. (1996)</td>
<td>Double-blind</td>
<td>I</td>
<td>66</td>
<td>292</td>
<td>72</td>
<td>N/A</td>
<td>Tsui</td>
<td>33</td>
<td>[25]</td>
</tr>
<tr>
<td>Poeve et al. (1998)</td>
<td>Double-blind</td>
<td>I</td>
<td>75</td>
<td>250–1000</td>
<td>81</td>
<td>N/A</td>
<td>Tsui, GIR (0–4)</td>
<td>10–32</td>
<td>[78]</td>
</tr>
<tr>
<td>Kessler et al. (1999)</td>
<td>Open-label</td>
<td>III</td>
<td>616</td>
<td>778</td>
<td>89</td>
<td>92</td>
<td>Tsui</td>
<td>&gt;60</td>
<td>[61]</td>
</tr>
<tr>
<td>Wissel et al. (2001)</td>
<td>Double-blind</td>
<td>II</td>
<td>68</td>
<td>500</td>
<td>86</td>
<td>49</td>
<td>Tsui, GIR (0–3)</td>
<td>41</td>
<td>[79]</td>
</tr>
<tr>
<td>Truong et al. (2005)</td>
<td>Double-blind</td>
<td>I</td>
<td>80</td>
<td>500</td>
<td>78</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>22</td>
<td>[80]</td>
</tr>
<tr>
<td>Truong et al. (2010)</td>
<td>Double-blind</td>
<td>I</td>
<td>116</td>
<td>500</td>
<td>91</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>36</td>
<td>[81]</td>
</tr>
<tr>
<td><strong>Xeomin® (BoNT-A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benecke et al. (2005)</td>
<td>Double-blind</td>
<td>II</td>
<td>463</td>
<td>140</td>
<td>N/A</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>40</td>
<td>[32]</td>
</tr>
<tr>
<td><strong>Myobloc®/Neurobloc® (BoNT-B)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lew et al. (1997)</td>
<td>Double-blind</td>
<td>I</td>
<td>122</td>
<td>10,000</td>
<td>77 (max.)</td>
<td>83 (max.)</td>
<td>TWSTRS</td>
<td>N/A</td>
<td>[48]</td>
</tr>
<tr>
<td>Brashear et al. (1999)</td>
<td>Double-blind</td>
<td>I</td>
<td>109</td>
<td>10,000</td>
<td>N/A</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>25</td>
<td>[49]</td>
</tr>
<tr>
<td>Brin et al. (1999)</td>
<td>Double-blind</td>
<td>I</td>
<td>77</td>
<td>10,000</td>
<td>N/A</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>21</td>
<td>[50]</td>
</tr>
<tr>
<td><strong>Comparison of BoNT-A versus BoNT-B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comella et al. (2005)</td>
<td>Double-blind</td>
<td>II</td>
<td>139</td>
<td>250/10,000</td>
<td>87/91</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>23/24</td>
<td>[51]</td>
</tr>
<tr>
<td>Tintner et al. (2005)</td>
<td>Double-blind</td>
<td>II</td>
<td>20</td>
<td>230/12,100</td>
<td>N/A</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>31/28</td>
<td>[52]</td>
</tr>
<tr>
<td>Pappert et al. (2008)</td>
<td>Double-blind</td>
<td>I</td>
<td>111</td>
<td>150/10,000</td>
<td>85/93</td>
<td>N/A</td>
<td>TWSTRS</td>
<td>19/25</td>
<td>[53]</td>
</tr>
</tbody>
</table>

*Fixed-dose, fixed-muscle injection.

*Comparative study of two Botox® preparations including only responders; pain reduction 52%.

BoNT: Botulinum toxin; GIR: Global improvement rating; Max.: Maximum; N/A: Not available; N/S: Not significant; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.
and one randomized, double-blind, crossover study comparing the clinical efficacy and safety of Dysport with Botox (NCT00950664). In addition, seven further studies, which have been completed but not yet published are listed (NCT00178945, NCT00702754, NCT00564681, NCT00549341, NCT00447772, NCT00015457, NCT00165776 and NCT00407030). Major features of these studies are summarized in Table 2. They include one prospective, double-blind, randomized, placebo-controlled trial evaluating efficacy and safety of Xeomin in BoNT-treated or toxin-naive patients (233 total), at doses of 120 or 240 U compared with placebo (NCT00407030) [Comella C, Jankovic J, Truong D, Hanschmann A, Graff S. Unpublished data]. This study showed, as expected, that Xeomin significantly improved TWSTRS total scores from baseline to week 4 with both dose regimens, with generally mild side effects, most frequently dysphagia, neck pain, and muscular weakness. This study had a double-blind extension phase over 48–68 weeks, which showed continued improvement in TWSTRS total scores and subscores [65]. Another large study aimed to analyze the effectiveness and safety in the treatment of the most frequent subtypes of CD, predominant rotational torticollis or predominant laterocollis, with a standard initial dose of 500 U Dysport, in a large representative group of de novo patients (n = 516; NCT00447772). This study showed that patients with both abovementioned major subtypes of CD improved equally well, measured by the Tsui score at week 4 and week 12, with generally low rates of expected side effects (muscular weakness: 13.6% and dysphagia: 9.9%). The authors concluded that the proposed treatment algorithm with a standardized, but at the same time individual injection protocol, was safe and effective in treating heterogeneous types of CD [66].

**Practical considerations**

Owing to the complex anatomy of the neck, with 54 different muscles influencing head and neck movements and shoulder position, and the highly variable clinical presentation of CD, a thorough clinical examination prior to the first BoNT treatment session, with detailed identification of appropriate target muscles and release of potential voluntary compensatory muscle activities in nondystonic muscles and preventive postures, is crucial to the success of BoNT therapy in CD patients. The choice of muscles to inject critically depends on the predominant head movement(s): turning, tilting, ante- or retro-collis and/or shoulder elevation (or a combination thereof). Commonly injected muscles include the sternocleidomastoid, splenius capitis, scalene (anterior, middle and posterior), semispinalis capitis, trapezius (upper portion), levator scapulae and infrahyoid muscles. Depending on the extent of dystonic muscle activity, injections may be required on one or both sides; in bilateral injections, a dose reduction is frequently necessary.

**Future perspective**

Currently available clinical studies on BoNT therapy for CD have extensively demonstrated the efficacy and safety of currently commercially available formulations of BoNT. Open questions pertain, mainly to attempt to establish approximate dose-conversion ratios of specific BoNT formulations, to the risk of development of nAbs associated with different BoNT formulations and to the most effective method for patient evaluation, including selection of which muscles to inject, especially concerning the routine use of electromyography (EMG)-and/or ultrasound-guided injections, and initial dosage for individual muscles. Although some studies suggest that the routine use of EMG-guided injections results in a greater magnitude of improvement [67] as opposed to injections based only on clinical examination, especially in patients with retrocollis, shoulder elevation and head tilt, in our experience, and as suggested by other experts, EMG-guided injections may be helpful in selected patients, but are not recommended on a routine basis. It is predicted that within the next 5 years more data will become available, especially on the risk of nAb formation and on attempts to establish approximate dose-conversion ratios, which will provide a basis for guidelines on the differential use of different BoNT formulations, both for toxin-naive patients, patients previously treated with BoNT and potentially for secondary nonresponders. It is possible that within the next 10 years more BoNT formulations will become commercially available, possibly resulting in a further reduced risk of nAb formation and possibly a reduced economic burden associated with BoNT treatment.

**Financial & competing interests disclosure**

Christoph Kamm has received speakers honoraria and research support from Merz Pharmaceuticals, Ipsen, Allergan, GlaxoSmithKline and Union Chimique Belge, and unrestricted travel grants from Ipsen Pharma and Merz Pharmaceuticals. Reiner Benecke has received speakers honoraria and research support from Merz Pharmaceuticals, Ipsen and Allergan. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
Table 2. Ongoing clinical studies assessing botulinum toxin formulation treatment in patients with cervical dystonia.

<table>
<thead>
<tr>
<th>Clinicaltrials.gov ID</th>
<th>Type of study</th>
<th>Sponsor</th>
<th>BoNT formulation</th>
<th>Phase</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actively recruiting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01056861</td>
<td>Case control</td>
<td>Henry Ford Health System/Allergan</td>
<td>Botox® (BoNT-A)</td>
<td>IV</td>
<td>To evaluate the effects of BoNT treatment on afferent sensory input using MEG</td>
</tr>
<tr>
<td>NCT00836017</td>
<td>Observational, case only</td>
<td>Allergan</td>
<td>Botox</td>
<td>IV</td>
<td>CD patient registry for the observation of BoNT-A efficacy</td>
</tr>
<tr>
<td>NCT00528541</td>
<td>RCT, double-blind, parallel</td>
<td>Allergan</td>
<td>Botox</td>
<td>IV</td>
<td>Comparison of efficacy and safety of Botox versus Dysport in moderate to severe CD</td>
</tr>
<tr>
<td>NCT00950664</td>
<td>RCT, double-blind, crossover</td>
<td>Seoul National University Hospital/Ipsen</td>
<td>Dysport® (BoNT-A)</td>
<td>IV</td>
<td>To examine the non-inferiority of Dysport in the clinical efficacy and safety, in comparison with Botox</td>
</tr>
<tr>
<td><strong>Completed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00178945</td>
<td>RCT, double-blind, crossover</td>
<td>Vanderbilt University</td>
<td>Botox</td>
<td>IV</td>
<td>To investigate the use of injections of Botox for the treatment of chronic neck pain</td>
</tr>
<tr>
<td>NCT00702754</td>
<td>Open-label</td>
<td>Solstice Neurosciences</td>
<td>Myobloc™ (BoNT-B)</td>
<td>IV</td>
<td>An open-label safety and immunogenicity study of Myobloc in patients with CD, with potential exposure for up to 7 years</td>
</tr>
<tr>
<td>NCT00564681</td>
<td>RCT, double-blind, parallel</td>
<td>Allergan</td>
<td>Botox</td>
<td>II</td>
<td>To investigate the use of the TWSTRS scale in a CD population treated with BoNT-A and placebo</td>
</tr>
<tr>
<td>NCT00549341</td>
<td>RCT, double-blind</td>
<td>Mentor Corporation</td>
<td>PurTox® (BoNT-A)</td>
<td>I</td>
<td>A single-dose escalation study to evaluate the safety of PurTox for the treatment of CD and to explore dose-associated efficacy</td>
</tr>
<tr>
<td>NCT00447772</td>
<td>Open-label</td>
<td>Ipsen</td>
<td>Dysport</td>
<td>III</td>
<td>To demonstrate equivalent efficacy and safety in the treatment of the two most frequent forms of CD (predominantly rotational torticollis and laterocollis) with the standard initial dose of 500 units Dysport</td>
</tr>
<tr>
<td>NCT00015457</td>
<td>RCT, double-blind, crossover</td>
<td>NINDS</td>
<td>N/A</td>
<td>II</td>
<td>To determine if amlodipine can augment the effect of BoNT injections in the treatment of focal dystonia</td>
</tr>
<tr>
<td>NCT00165776</td>
<td>RCT, double-blind, parallel</td>
<td>Eisai Limited</td>
<td>E2014 (BoNT-B)</td>
<td>II</td>
<td>To evaluate efficacy and safety of E2014 (2500, 5000 and 10000 U) compared with placebo</td>
</tr>
<tr>
<td>NCT00407030</td>
<td>RCT, double-blind, parallel</td>
<td>Merz Pharmaceuticals</td>
<td>Xeomin® (BoNT-A)</td>
<td>III</td>
<td>IncobotulinumtoxinA (Xeomin) versus placebo in the treatment of CD</td>
</tr>
</tbody>
</table>

BoNT: Botulinum toxin; CD: Cervical dystonia; MEG: Magnetoencephalography; N/A: Not available; NINDS: National Institute of Neurological Disorders and Stroke; RCT: Randomized controlled trial; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.
Review: Clinical Trial Outcomes

Kamm & Benecke

Executive summary

Serotypes of botulinum toxin & commercially available preparations

- Seven distinct immunological serotypes can be differentiated, classified into A–G. All commercially available botulinum toxin (BoNT) preparations currently available are either based upon BoNT-A or upon BoNT-B.
- According to currently available data, it is thought that Botox® and Xeomin® are highly similar with respect to their therapeutic effects and profile of side effects in clinical practice.
- The dose conversion ratio of Botox versus Xeomin appears to be 1:1, whereas that between Botox and Dysport® is estimated to be between 1:3 and 1:4, and that between Botox and Myobloc™/Neurobloc® between 1:40 and 1:50. However, in clinical practice, the treating physician must be aware that each brand is unique and that simple dose ratios are not applicable; therefore, caution should be used, especially when it is necessary to switch between different brands in a given patient.
- Xeomin is a relatively new BoNT-A containing only the active neurotoxin without accessory (complexing) proteins.

Clinical studies with BoNT-A

- BoNT, in properly adjusted doses, is an effective and safe treatment of cervical dystonia (CD), should be offered as a treatment option to patients with cervical dystonia (level A) and is probably more efficacious and better tolerated in patients with CD than trihexyphenidyl (level B).
- Long-term studies have demonstrated continuous efficacy of BoNT treatment for >12 years and generally low immunogenicity of BoNT-A.

Clinical studies with BoNT-B

- BoNT-B is safe and efficacious in the management of CD, but has a more disadvantageous profile of side effects and a noted higher antigenicity compared with BoNT-A.
- Most experts currently suggest that BoNT-A should be considered the front-line treatment for CD and that BoNT-B should primarily be considered as an option for patients who have developed neutralizing antibodies against BoNT-A.

Bibliography

Botulinum toxin therapy for cervical dystonia

Review: Clinical Trial Outcomes


Website

101 Clinical trials.gov

www.clinicaltrials.gov