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Review

Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders

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ABSTRACT

Botulinum neurotoxin (BoNT) can be injected to achieve therapeutic benefit across a large range of clinical conditions. To assess the efficacy and safety of BoNT injections for the treatment of certain movement disorders, including blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, focal limb dystonias, laryngeal dystonia, tics, and essential tremor, an expert panel reviewed evidence from the published literature. Data sources included English-language studies identified via MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Central Register of Controlled Trials. Evidence tables generated in the 2008 Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for movement disorders were also reviewed and updated. The panel evaluated evidence at several levels, supporting BoNT as a class, the serotypes BoNT-A and BoNT-B, as well as the four individual commercially available formulations: abobotulinumtoxinA (A/Abo), onabotulinumtoxinA (A/Ona), incobotulinumtoxinA (A/Inco), and rimabotulinumtoxinB (B/Rima). The panel ultimately made recommendations for each therapeutic indication, based upon the strength of clinical evidence and following the AAN classification scale. For the treatment of blepharospasm, the evidence supported a Level A recommendation for BoNT-A, A/Inco, and A/Ona; a Level B recommendation for A/Abo; and a Level U recommendation for B/Rima. For hemifacial spasm, the evidence supported a Level B recommendation for BoNT-A and A/Ona, a Level C recommendation for A/Abo, and a Level U recommendation for A/Inco and B/Rima. For the treatment of oromandibular dystonia, the evidence supported a Level C recommendation for BoNT-A, A/Abo, and A/Ona, and a Level U recommendation for A/Inco and B/Rima. For the treatment of cervical dystonia, the published evidence supported a Level A recommendation for all four BoNT formulations. For limb dystonia, the available evidence supported a Level B recommendation for both

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A/Abo and A/Ona, but no published studies were identified for A/Inco or B/Rima, resulting in a Level U recommendation for these two formulations. For adductor laryngeal dystonia, evidence supported a Level C recommendation for the use of A/Ona, but a Level U recommendation was warranted for B/Rima, A/Abo, and A/Inco. For the treatment of focal tics, a Level U recommendation was warranted at this time for all four formulations. For the treatment of tremor, the published evidence supported a level B recommendation for A/Ona, but no published studies were identified for A/Abo, A/Inco, or B/Rima, warranting a Level U recommendation for these three formulations. Further research is needed to address evidence gaps and to evaluate BoNT formulations where currently there is insufficient or conflicting clinical data.

1. Introduction

The therapeutic use of botulinum neurotoxin (BoNT) has evolved from its initial application in the treatment of movement disorders, such as blepharospasm and other dystonias, to many other neurologic and non-neurologic disorders. This review will evaluate the evidence for the therapeutic application of BoNT to blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, focal limb dystonias, laryngeal dystonia, tics, and essential tremor.

In general, the therapeutic benefits of BoNT in movement disorders derive from its inhibitory actions on muscle contraction resulting from blockade of acetylcholine at the neuromuscular junction (Mayer and Esquenazi, 2003; Sheean, 2003). Accordingly, the primary effect of BoNT is relaxation of the affected skeletal muscle. However, considerable evidence suggests that BoNT injected peripherally may also influence central nervous system function (Gracies, 2004). By blocking gamma as well as alpha motor neurons, there is denervation of intrafusal muscle fibers (Giladi, 1997). This reduces muscle spindle afferent input to the central nervous system and thereby modifies sensorimotor and proprioceptive pathways (Giladi, 1997; Hallett, 2000; Rosales and Dressler, 2010). These mechanisms may contribute to the therapeutic effects of BoNT in focal dystonias beyond the effects anticipated on the basis of muscle relaxation alone.

1.1. Objectives

The aim of this review of evidence is to assess the effectiveness of BoNT injections for the treatment of movement disorders; the intent is to evaluate both the class- and formulation-specific effects of BoNT when the evidence allows. Two BoNT serotypes (A and B) are approved by the Food and Drug Administration (FDA) for clinical use in the United States. Approved BoNT-A formulations are onabotulinumtoxinA (A/Ona; Allergan, Inc.), abobotulinumtoxinA (A/Abo; Ipsen Limited), and incobotulinumtoxinA (A/Inco; Merz Pharmaceuticals); the only approved BoNT-B formulation is rimabotulinumtoxinB (B/Rima; Solstice Neurosciences, LLC). These agents are marketed under the brand names Botox®, Dysport®, Xeomin®, and Myobloc®/Neurobloc®, respectively.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

All studies comparing BoNT injection or BoNT injection plus other pharmacologic and nonpharmacologic therapies to placebo, no treatment, or active comparators, or comparing doses, of BoNT were considered.

2.1.2. Types of subjects

Adults and children were included, as appropriate, based on each of the specific therapeutic indications of interest.

2.1.3. Types of interventions

Separate sections of the evidence tables were created for assessments of 1) effectiveness (placebo-controlled studies), 2) comparative effectiveness (active-controlled studies comparing different doses or formulations of BoNT or different pharmacologic therapies to BoNT), and 3) methodology, defined as studies comparing different modes of administration including location, type of imaging and other forms of guidance for injection, and nonpharmacologic treatments.

2.1.4. Types of outcome measures

From the studies reviewed, a variety of outcome measures were identified as potential measures of effectiveness for each disease/disorder of interest. Outcome measures could include variables related to body functions and body structures as well as patient- and/or investigator-reported outcomes such as health-related quality of life and perceived improvements. Generally placebo responses in these disorders are small or absent.

2.2. Search methods for identification of studies

The following terms were used to search several databases including MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Controlled Trials Register. Clinicaltrials.gov was also searched for additional studies that may not have been indexed in the former databases as of the cutoff data for inclusion (March 1, 2011). Only English-language articles were considered. Articles that were included were fully published (i.e., online and in print) or available as full text online in peer-reviewed

publications. The search terms used were *botulinum toxin* (see below) and terms relevant to specific disorders of interest. In addition to the search terms for BoNT and those specific to each of the therapeutic applications of interest, the following criteria were imposed: 1) relevance to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Mechanistic studies, abstracts, reviews, and meta-analyses were excluded as primary sources; however, publications of these types were searched manually for possible primary studies not detected by database searches.

The following search strategy was adapted as needed to accommodate the particulars of each of the databases:

1. Botulinum toxin/
2. Botulinum neurotoxin/
3. BoNT
4. Botulinum toxin type a/
5. Botulinum toxin type b/
6. Botulin$.tw
7. Botox.tw
8. Dysport.tw
9. Myobloc; Neurobloc
10. Xeomin; NT 201
11. Onabotulinum
12. Rimabotulinum
13. Incobotulinum
14. Abobotulinum
15. Or/1–12

In addition, the results of the BoNT search were filtered with search terms relevant to the disease/disorders of interest. The current article reviews the use of BoNT for the following movement disorders: cervical dystonia, focal limb dystonia, blepharospasm, hemifacial spasm, tics, laryngeal dystonia, and oromandibular dystonia. The following search terms were used to identify trials:

1. Movement disorder
2. Blepharospasm; Meige syndrome
3. Hemifacial spasm
4. Tics
5. Dystonia; cervical; torticollis; spasmodic
6. Limb dystonia, hand dystonia; focal dystonia; writers' cramp
7. Laryngeal dystonia; dysphonia; spasmodic; laryngospasm
8. Essential hand tremor; essential tremor
9. Oromandibular dystonia; temporomandibular; nocturnal bruxism; bruxism
10. Or/1–9

2.3. Data collection and analysis

2.3.1. Selection of trials

Evidence tables generated in the 2008 Report of the Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for movement disorders (Simpson et al., 2008) were used as a starting point. The literature search described above was conducted to update and expand the database, to identify studies published since the TTA project.

2.3.2. Quality of trials

A centralized review staff evaluated the methodologic quality of the included trials according to a modification of the American Academy of Neurology (AAN) quality of evidence scale classification. Studies previously classified by the TTA and identified in the present review as possibly requiring revised classification were separated for reassessment. Both the group of newly identified studies and the group of TTA studies for reassessment received second reviews by members of the expert panel. Each member of the subcommittee accepted responsibility for oversight of an entire category of movement disorders. Differences of opinion were resolved by panel consensus.

The AAN classification (see AAN classification of evidence for therapeutic intervention on the NeurologyWeb site at http://www.aan.com/globals/axon/assets/2371.pdf) is shown below:

AAN Classification of Quality of Evidence for Clinical Trials

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population.

The following are required:

a. Primary outcome(s) clearly defined
b. Exclusion/inclusion criteria clearly defined
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
d. Relevant baseline characteristics presented and substantially equivalent among treatment groups, or appropriate statistical adjustment for differences
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
    4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomized controlled trial in a representative population that lacks one criterion from a–d.[1]

[1] Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the study is automatically downgraded to Class III.

Class III: All other controlled trials including well-defined natural history controls or patients serving as own controls in a representative population, where outcome assessment is independently assessed or independently derived by objective outcome measurement.[2]

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

In adapting these criteria to the present assessment, the panel considered that absence of reporting of the rate of premature study discontinuation or any information regarding safety at the time point for the primary outcomes assessment (i.e., not during open-label extension or long-term follow-up) warranted a downgrade in classification for studies otherwise meeting the requirements for Class 1 evidence. Furthermore, a premature discontinuation rate greater than 20% was considered to downgrade a trial otherwise deemed Class I evidence to Class II.

The criteria for Class I studies do not preclude active-comparator trials. However, the absence of a placebo control renders it difficult to estimate the effect size and hence the quantitative efficacy of either active treatment. To address this challenge, the panel considered, in addition to whether active-comparator studies met their pre-specified outcomes, the clinical relevance of the changes in outcome parameters within treatment groups.

2.4. Description of the analytic process

A panel comprised of specialists with experience in the therapeutic uses of BoNT for the indications under consideration or with expertise in basic and translational aspects of BoNT participated in the assessment was convened for this review. Panel members were selected because of their expertise with neurotoxin therapy as evidenced by years of clinical experience, participation in clinical trials, authorship of peer-reviewed literature, and/or prior involvement with guidelines methodology. The panel reviewed evidence tables and, based on the strength of evidence regarding the quality and quantity of evidence regarding the efficacy and safety of BoNT for each therapeutic indication, made a recommendation according to the AAN classification scale.

2.4.1. Classification of recommendations

A Established as effective, ineffective, or harmful for the given condition in the specified population (Level A rating requires at least two consistent Class I studies)

B Probably effective, ineffective, or harmful for the given condition in the specified population (Level B rating requires at least one Class I study or at least two consistent Class II studies)

C Possibly effective, ineffective, or harmful for the given condition in the specified population (Level C rating requires at least one Class II study or two consistent Class III studies)

U Data inadequate or conflicting; given current knowledge, treatment is unproven

If there were two or more Class I studies for an individual product, there was no need to consider Class II studies unless they provided additional insights regarding dosing, differences between brands, or other unique attributes. In the event that there was only one placebo controlled Class I study, a Class I comparator trial could provide confirmatory support if the reviewers considered the efficacy to be clinically meaningful. If only one Class I study was available, multiple Class II studies were considered. For a specific BoNT serotype, if insufficient quality evidence existed by individual brand but consistent results were observed across brands, recommendations were applied to the serotype. Recommendations for individual formulations must not be extrapolated to other brands.

The serotype and brand of BoNT used in specific studies are provided in the evidence tables. When sufficient evidence was available for each serotype and brand, the panel provided brand.

3. Results

3.1. Blepharospasm

Both A/Ona and A/Inco are approved for the treatment of blepharospasm. The FDA approval of A/Ona for the treatment of blepharospasm in 1989 was based largely on uncontrolled, open-label observations in which the efficacy was deemed to be so dramatic that there was little compelling need to develop an evidence base of controlled clinical trials. In fact, the current A/Ona prescribing information includes three studies supporting the blepharospasm indication: an open-label, historic control study in 27 patients; a double-blind, placebo-controlled study in 12 patients; and an open-label study in 1684 patients (Botox [Package Insert], 2010).

The currently available evidence supporting the use of BoNT-A for blepharospasm consists of three Class I trials (Jankovic et al., 2011; Roggenkamper et al., 2006; Wabbels et al., 2011), four Class II trials (Girlanda et al., 1996; Jankovic and Orman, 1987; Nussgens and Roggenkamper, 1997; Truong et al., 2008), and one Class III trial (Sampaio et al., 1997), with a total of 866 patients (see Table 1). The outcome measures included accepted, disease-specific rating scales such as the Jankovic rating scale, the Blepharospasm Disability Index (BSDI), and several subject–controlled (Girlanda et al., 1996; Jankovic et al., 2011; Jankovic and Orman, 1987; Truong et al., 2008) and four were active-comparator trials (Nussgens and Roggenkamper, 1997; Roggenkamper et al., 2006; Sampaio et al., 1997; Wabbels et al., 2011). An additional Class III trial comparing two BoNT dilutions (Boyle et al., 2009) was excluded from the evaluation but provided practical insights into the administration of BoNT. One of the placebo-controlled studies used a within-patient comparative design, with one eye serving as the control

[2] Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Table 1
Blepharospasm.

Ref	AAN class	Design	*N*	Treatment (serotype/ brand//dose)	Follow-up	Outcome measures (1-primary, 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo-controlled										
Jankovic et al., 2011	I	R, DB, PC	109 previously treated ≥2 times w/BoNT-A other than A/Inco	A/Inco up to 50 U/eye or matched PBO	≤20 w	1-JRS at 6 w 2-BSDI, PEGR	6%	AEs in 70.3% A/Inco vs. 58.8% PBO; most common AEs: ptosis, dry eye, dry mouth; generally well tolerated	1-JRS improved significantly more with Inco (−0.83 vs. +0.21; $p < 0.001$). 2-Significantly greater improvement in BSDI for A/Inco vs. PBO ($p = 0.002$). Other outcomes also favored A/Inco.	Safety assessments included systemic toxin spread. Registration study; basis for FDA approval
Truong et al., 2008	II	R, DB, PC, parallel	120	A/Abo 40, 80, 120 U/eye vs. PBO in bilateral BEB	16 w	1-PNA on BDS (difference in median PNA between active treatment and PBO) at 4 w 2-Functional disability on FIM at 8, 12, 16 w; severity of ocufacial spasms; VAS global impairment	(28/120) 14/28 PBO vs. 14/92 A/Abo	Most AEs mild to moderate; most common: ptosis, blurred vision, tearing, lagophthalmos, dry eyes, diplopia; AEs dose-related and more frequent in active arms	1-PNA significantly better in active arms vs. PBO ($p < 0.01$). 2-Greater functional improvement with A/Abo vs. PBO ($p < 0.001$). 80 U appeared to be optimal dose of A/Abo.	>20% D/C
Girlanda et al., 1996	II	SB, PC (within-pt comparator)	6	A/Ona 20 U/ eye vs. PBO in other eye	1 mo	Subjective scale in blinded video rating	0	NA	Reduction in blepharospasm in active-treated eye.	Small sample; not specified how or if randomized; no safety information
Jankovic and Orman, 1987	II	R, DB, PC	12	A/Ona (oculinum) or PBO ($n = 5$); 25 U/eye, then 50 U/eye if ineffective	Not clear	Severity using Fahn scale; pt subjective scale	0	Blurred vision, tearing, ptosis, ecchymosis	Improvement on both scales in all A/Ona pts	Randomization by coin toss; small cohort
Comparative: active comparator										
Wabbels et al., 2011	I	R, DB, parallel, active comparator	65 BEB pts who had received A/Ona ≥20 U/eye	A/Ona to A/Inco 1:1 dose ratio at dose of most recent treatment (~20 U/eye); mean dose A/Ona 29 U/eye; A/Inco 27 U/eye	14 w	1-BSDI change at 4 w 2-BSDI at 8 w, PGAS at 4 w, JRS at 4 and 8 w	1/treatment arm	No difference in AEs	1-Both products similarly effective.	
Roggenkamper et al., 2006	I	R, DB, parallel group	300	A/Ona total 40.8 U (mean); A/Inco total, 39.6 U (mean)	16 w	1-Changes in total BSDI score at 4 w 2-Change in BSDI at 8 w, JRS at 4 and 8 w, PGAS at 4 w	44	Similar AEs; most common AE was ptosis, 6.08% A/Inco vs. 4.52% A/Ona	Similar efficacy on primary and secondary end points. Mean duration of benefit 110 d for both groups.	
Nussgens and Roggenkamper, 1997	II	R, DB, cross-over	212	A/Ona 45.4 U, A/Abo 182.1 U	5 mo	Duration of effect	NA	All AEs: A/Ona 17%, A/Abo 24% ($p = 0.05$); ptosis (A/Abo 6.6% vs. A/Ono 1.4%; $p < 0.01$), tearing, blurred vision, diplopia, hematoma, foreign body sensation	Similar duration of effect (~8 w).	Similar efficacy

Sampaio et al., 1997	III	R, SB, parallel, active comparator	42	A/Abo 100 U; A/Ona 25 U; booster (similar doses) allowed at 1 mo	3–4 mo	1-Duration of effect, number of boosters needed 2-Latency of effect, clinical efficacy, AEs	2	All AEs: A/Abo 50%, A/Ona 47%; most common AE: incomplete ptosis	Duration similar for both formulations: A/Abo 13 w, A/Ono 11 w (p NS).	Results not differentiated by indication (blepharospasm or hemifacial spasm); rater not blinded
Ochudlo et al., 2007	IV	Active comparator, not randomized, not blinded	33	A/Abo 125 U, A/Ona 25 U	3–4 mo	SF36 (QoL); MADRS depression scale; Unified Dystonia Rating scale	NA	1 transient, 2 diplopia	All parameters improved, both treatments pooled.	The two brands not compared; dosing ratio 5:1
Methodologic study										
Boyle et al., 2009	III	R, within-pt comparison, crossover	16	A/Ona 100 U/mL in 1 eye, 10 U/mL in other eye	8 mo	Pain, bruising, redness postinjection; complications at follow-up (ptosis, diplopia, tearing, dry eye), duration of relief, side preferred	0	Ptosis, tearing, dry eye (NS)	58% reduction in perceived pain with 100 U ($p < 0.001$); no differences in bruising, redness.	Dilution study; outcomes were generally safety variables

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; AE, adverse event; A/Inco, incobotulinumtoxinA; A/Ona, onabotulinumtoxinA; BDS, blepharospasm disability scale; BEB, benign essential blepharospasm; BoNT-A, botulinumtoxinA; BSDI, blepharospasm disability index; DB, double blind; D/C, discontinuations; FIM, frequency of involuntary movement; JRS, Jankovic Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; PC, placebo-controlled; PEGR, Patient Evaluation of Global Response; PGAS, Physician Global Assessment Scale; PNA, percentage of normal activity; R, randomized; SB, single blind; VAS, visual analog scale.

for the contralateral A/Ona-treated eye within the same patient (Girlanda et al., 1996). The study showed greater reduction in blepharospasm on the A/Ona-treated side, but it was deemed Class II evidence because the sample was small (six patients), the process for random allocation of treatment to eyes was not specified, and no safety data were included in the publication. Another randomized, placebo-controlled trial, which included several A/Abo doses (Truong et al., 2008), was categorized as Class II because of an unexpected high rate of premature discontinuations (28/120 patients total), mainly within the placebo arm (14/28). The most recent placebo-controlled trial (Class I) evaluated A/Inco in 109 patients with blepharospasm who had previously been treated at least twice with a different BoNT-A formulation; patients in the current trial noted statistically significant improvement in all outcome measures with active treatment but not in the placebo arm (Jankovic et al., 2011). In this study, the patients were randomized in a 2:1 ratio to A/Inco or placebo; 94% completed the 20-week study. A significant difference was observed in the primary efficacy variable (change in Jankovic Rating Scale severity subscore) favoring A/Inco (95% confidence interval, 0.5–1.4; $p < 0.001$). Functional impairment, as measured by the BSDI, and all secondary outcome measures also significantly favored A/Inco compared with placebo. Adverse events (AEs) were reported in 70.3% of A/Inco patients and 58.8% of placebo patients and included eyelid ptosis (18.9% vs. 5.9%), dry eye (18.9% vs. 11.8%), and dry mouth (14.9% vs. 2.9%). This was a registration study and was the sole basis for FDA approval of A/Inco for the treatment of blepharospasm (Xeomin [Package Insert], 2010).

Two active-comparator studies (both Class I) compared A/Ona and A/Inco (Roggenkamper et al., 2006). These studies were 14 and 16 weeks in duration, with primary outcomes assessed at 4 weeks postinjection in both. The mean doses were similar for the two BoNT-A formulations in both studies (40.8 U and 58.9 U). No remarkable differences were noted between the two brands with respect to either efficacy or tolerability.

A/Ona and A/Abo were compared in two studies of patients with blepharospasm using a 1:4 dosing ratio of A/Ona to A/Abo. One of these trials (Class II) used a crossover study design in 212 patients (Nussgens and Roggenkamper, 1997), while the other (Class III) used a parallel-group design in 42 patients without blinded evaluations (Sampaio et al., 1997). In both studies, the primary outcome, durability of effectiveness, did not differ significantly between the two BoNT-A formulations. Secondary outcomes and safety and tolerability were also comparable between the two formulations.

3.1.1. Summary

In the aggregate, studies of BoNT-A show level A evidence supporting effectiveness for the treatment of blepharospasm. This recommendation is based on one Class I placebo-controlled study of A/Inco (Jankovic et al., 2011), two Class I studies comparing A/Ona and A/Inco (Roggenkamper et al., 2006; Wabbels et al., 2011), and three Class II studies, one of A/Abo (Truong et al., 2008) and two using A/Ona (Girlanda et al., 1996).

For the individual formulations, the available evidence supports a level A recommendation for A/Inco based on one Class I placebo-controlled trial (Jankovic et al., 2011) and two Class I active-comparator trials (Roggenkamper et al., 2006; Wabbels et al., 2011); a level A recommendation for A/Ona based on two Class I active-comparator trials (Roggenkamper et al., 2006; Wabbels et al., 2011), two Class II placebo-controlled trials (Girlanda et al., 1996; Jankovic and Orman, 1987), and one Class II active-comparator trial (Nussgens and Roggenkamper, 1997); and a level B recommendation for A/Abo based on two Class II trials, one placebo controlled (Truong et al., 2008) and one active comparator (Nussgens and Roggenkamper, 1997). No published studies were identified using B/Rima for blepharospasm, which warrants a Level U recommendation for that formulation.

3.1.2. Evidence gaps and recommendations for further studies

There are no quality data for BoNT-B for the treatment of blepharospasm, but it is likely that its efficacy is similar to that of BoNT-A. There are few data from controlled trials regarding optimal dosing. In light of the long-standing acceptance of BoNT for first-line therapy for blepharospasm, it is reasonable to consider empirically derived dosing recommendations from expert opinion based on clinical experience. Although some open-label data indicate that pretarsal injection may be beneficial in patients with apraxia of eyelid opening, particularly if it is triggered by blepharospasm (Forget et al., 2002; Jankovic, 1996), more studies are needed to explore the role of BoNT in the treatment of this disorder.

3.2. Hemifacial spasm

There were two placebo-controlled studies evaluating the efficacy of A/Ona for the treatment of hemifacial spasm: one Class II study in 11 patients (Yoshimura et al., 1992b) and a Class III study in 101 patients (Park et al., 1993) (see Table 2). The Class II, placebo-controlled study assessed three active doses individualized in a crossover design (Yoshimura et al., 1992b). The follow-up was 1 month, and the outcomes consisted of blinded ratings of videotapes and subjective patient ratings of improvement. Three of eleven patients discontinued prematurely, but partial data were included in the analysis. Objective improvement was noted in 84% of subjects after A/Ona injections, with a trend for better response to the higher dose, compared with 38% of subjects who showed improvement after placebo injection. Subjective improvement was reported in 79% of subjects after injections with BoNT, regardless of dose. The most common side effect was facial weakness, noted after 97% of active injections. Facial bruising (20%), diplopia (13%), ptosis (7%), headache (7%), and various other mild side effects occurred less frequently.

An additional Class II, single-blind study compared A/Ona and A/Abo in a total of 49 patients (Sampaio et al., 1997). The primary outcome, duration of effect and number of booster doses required at 1 month, was comparable between the two toxins. Premature discontinuations appeared to be somewhat less common with A/Ona (6/22) compared with A/Abo (12/27), but this difference did not reach statistical significance. Any AE occurred in comparable proportions of patients treated with the two toxins (47% and 50% for A/Ona and A/Abo, respectively), with facial paresis the most commonly reported AE.

A Class III study (Park et al., 1993) initially evaluated A/Ona in 8 patients who were randomly assigned to receive either BoNT or placebo in a double-blind design; improvement was seen in patients who received active treatment, but no improvement was observed in those who received placebo. Subsequently 93 additional patients were included in an open-study design, and all patients in the open study showed improvement. One Class III study evaluated B/Rima doses of 100, 200, 400, or 800 U in sequential fashion (Trosch et al., 2007). All doses except the 100 U dose reduced hemifacial severity; these improvements tended to return to baseline by 8 weeks postinjection. B/Rima was fairly well tolerated, with no pattern of serious AEs or AEs that led to permanent study discontinuation.

3.2.1. Summary

The available evidence supports a level B recommendation for BoNT-A for the treatment of hemifacial spasm, based on two Class II studies (Sampaio et al., 1997; Yoshimura et al., 1992b). For the individual formulations, the available evidence supports a level B recommendation for A/Ona based on two Class II studies (Sampaio et al., 1997; Yoshimura et al., 1992b) and a level C recommendation for A/Abo based on one Class II study (Sampaio et al., 1997). There are insufficient data for A/Inco and B/Rima, which warrants a Level U recommendation for each of these two formulations.

3.2.2. Evidence gaps and recommendations for future studies

There have been no studies of A/Inco, and there is insufficient evidence to recommend B/Rima for the treatment of hemifacial spasm. Further studies are also needed to serve as the basis for the available BoNT-A formulations individually. Additionally, studies are needed not only in typical hemifacial spasm, presumably caused by vascular compression of the facial nerve, but also for other facial spasms (Yaltho and Jankovic, 2011).

3.3. Oromandibular dystonia

One Class II study of 8 patients evaluated the efficacy and safety of A/Ona for the treatment of oromandibular dystonia (see Table 3) (Jankovic and Orman, 1987). For this therapeutic application, BoNT-A was well tolerated and produced improvement in subjective ratings of pain and symptom severity. In another Class II study, 12 subjects with nocturnal bruxism, which may be considered a form of jaw-closure dystonia, were randomized to receive either A/Abo (80 U) or saline placebo (Lee et al., 2010). Nocturnal electromyographic activity was recorded during sleep from masseter and temporalis muscles before injection and 4, 8, and 12 weeks after injection; bruxism symptoms were investigated using questionnaires. In the BoNT injection group, bruxism events decreased significantly in the masseter muscle ($p = 0.027$) but not in the temporalis muscle; subjective bruxism symptoms decreased in both groups after injection ($p < 0.001$).

Table 2
Hemifacial spasm.

Ref	AAN class	Design	*N*	Treatment (serotype/ brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo controlled										
Yoshimura et al., 1992a	II	DB, PC, prospective	11	A/Ona individualized doses (5–90 U) or PBO	1 mo	Blinded rating of videotapes and pt subjective scale	3	Facial weakness (97%), extraocular muscle weakness, diplopia, ptosis, blurred vision	Blinded videotape review: 84% improved in all dose groups vs. 11% in PBO group; 79% subjective improvement (72% substantial) over all doses vs. 11% in PBO group. Degree of response was dose related.	
Comparator: active comparator or multiple doses										
Sampaio et al., 1997	II	SB, R, parallel group	49	A/Abo 70 U, A/Ona 17.5 U; booster (similar doses) allowed at 1 mo	3–4 mo	1-Duration of effect, number of booster doses needed 2-Latency of effect, clinical efficacy	18	AEs: A/Abo 50%; A/Ona 47%; most common AE: facial paresis	Duration similar for both formulations: A/Abo 13 w, A/Ono 11 w (*p* NS).	Results not differentiated by indication (blepharospasm or hemifacial spasm); rater not blinded
Park et al., 1993	III	Open-label, PC	101	A/Ona (Oculinum; mean, 13.5 U/pt) or PBO	7–20 mo	Intensity of facial and orbicularis muscle spasm	N/A	Mild complications in 63%: dry eye (19.8%), mouth droop (19.8%), ptosis (10.9%)	Mean duration, 16.5 w; mean peak effect at 4 d, improvement in active but not in PBO group.	
Trosch et al., 2007	III	SB, open-label	24	B/Rima 100, 200, 400, or 800 U, sequentially	88 d (range, 41–332)	1-Safety and treatment-emergent AEs (via pt social impairment VAS, pt severity of contraction VAS, physician- and pt-assessed HFS frequency and severity 2-Dose finding	2	9 treatment-emergent AEs	Reduction in all outcomes with doses >200 U but return to baseline 4–8 w postinjection. Social impairment mean scores higher than baseline at 8 w. Physician-assessed HFS showed sustained decrease in 400 U and 800 U groups through 8 w.	

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; AE, adverse event; A/Ona, onabotulinumtoxinA; BL, baseline; B/Rima, rimabotulinumtoxinB; DB, double blind; D/C, discontinuations; HFS, hemofacial spasm; PBO, placebo; PC, placebo-controlled; R, randomized; SB, single blind; VAS, visual analog scale.

Table 3
Oromandibular dystonia.

Ref	AAN class	Design	*N*	Treatment (serotype/brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Lee et al., 2010	II	R, DB, PC	12 with nocturnal bruxism	A/Abo 80 MU or PBO at 3 sites in both masseters	12 w	1-Number of EMG bruxism events (masseter and temporalis muscles) at 4, 8, 12 w 2-Bruxism symptoms	0	No AEs reported	1-Bruxism events in masseter but not temporalis muscle decreased significantly with A/Abo vs. PBO. 2-Subjective bruxism symptoms decreased in both groups.	
Jankovic and Orman, 1987	II	R, DB, PC	8 with oromandibular-CD	A/Ona (oculinum) 52.8 U, mean or PBO	Not clear	Severity using Fahn scale; pt subjective scale	0	1 each of headache, sore throat, dysarthria, dysphagia	3/8 A/Ona patients improved (20.1% improvement on examiner's rating scale, 6.7% improvement on self-assessment, 20.0% improvement on videotape rating). Mean peak effect 1.1, with 5.6-w duration.	Randomization by coin toss; small cohort

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; AE, adverse event; A/Ona, onabotulinumtoxinA; CD, cervical dystonia; DB, double blind; D/C, discontinuations; EMG, electromyography; MU, mouse units; PBO, placebo; PC, placebo-controlled; R, randomized.

3.3.1. Summary

One Class II trial (Jankovic and Orman, 1987) provides evidence to support a level C recommendation for the use of BoNT-A for the treatment of oromandibular dystonia. For the individual formulations, the available evidence supports a level C recommendation for A/Ona based on one Class II study (Jankovic and Orman, 1987) and a level C recommendation for A/Abo for a possible variant of oromandibular dystonia manifested by bruxism, based on another Class II study (Lee et al., 2010). No published studies were identified for A/Inco or B/Rima, which results in a Level U recommendation for these two formulations.

3.3.2. Evidence gaps and recommendations for future studies

There is a need for further evaluation of other BoNT formulations for treatment of this disorder and for additional studies in patients with oromandibular dystonia, manifested by jaw closure (often associated with clenching, trismus, and bruxism), jaw deviation, and jaw opening.

3.4. Cervical dystonia

There is abundant high-quality, placebo-controlled evidence supporting the efficacy of BoNT for cervical dystonia (CD): one Class I study for A/Ona (Botox [Package Insert], 2010; Geenen et al., 1996) three Class I studies for A/Abo (Poewe et al., 1998; Truong et al., 2010, 2005), three Class I studies for B/Rima (Brashear et al., 1999; Brin et al., 1999; Lew et al., 1997), and a single Class I study of A/Inco (Comella et al., 2011) (see Table 4).

The duration of follow-up in these studies ranged from 8 weeks to 20 weeks. The primary outcome in most of these studies was the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (Brashear et al., 1999; Brin et al., 1999; Comella et al., 2011; Lew et al., 1997; Truong et al., 2010, 2005). One exception is the unpublished data from the A/Ona phase 3 registration study, which served as the basis for FDA approval of A/Ona for the CD indication (Botox [Package Insert], 2010). The dual primary outcome in this study, as noted in the Prescribing Information, was the Cervical Dystonia Severity Scale, which provides a quantitative measurement of the change in turn, tilt, or shift after treatment (O'Brien et al., 2001), and improvement on the Physician Global Assessment Scale. In two Class I placebo-controlled studies of B/Rima, a dose–response relationship was noted both for efficacy and AEs (Brashear et al., 1999; Lew et al., 1997), while the third Class I trial used a single B/Rima dose of 10,000 U (Brin et al., 1999).

The basis for FDA approval of A/Inco to reduce the symptoms of CD was the placebo-controlled, parallel-group, double-blind study of A/Inco in 233 patients randomly assigned to receive a single treatment of A/Inco 120 U or 240 U or placebo (Xeomin [Package Insert], 2010; Comella et al., 2011). For patients previously treated with BoNT, there was a washout period of at least 10 weeks. The primary outcome was the change from baseline in the TWSTRS total score (comprised of severity, disability, and pain subscales) at 4 weeks postinjection. Patients were followed for up to 20 weeks after treatment, until they required an additional treatment. There were no significant systematic differences between the responses of patients

Table 4
Cervical dystonia.

Ref	AAN class	Design	*N*	Treatment (serotype/brand/dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo controlled										
Truong et al., 2010	I	R, DB, PC	116	500 U A/Abo or PBO	12 w for DB, option to enter open extension	1-Change in TWSTRS total score at 4 w 2-Change in TWSTRS total scores at 8 and 12 w; change on VAS for symptom severity (investigator and pt ratings); SF-36 at 8 w; % of treatment success at 12 w	10 BoNT, 23 PBO	Any AE: 47% A/Abo, 44% PBO; most common AEs, dysphagia (5 A/Abo) and injection site pain (3 A/Abo, 2 PBO); 1 SAE in PBO; most AEs mild to moderate	1-A/Abo reduced TWSTRS total at w 4 more than PBO (-15.6 ± 2.0 vs. -6.7 ± 2.0; $p < 0.001$) 2-Significant improvement in TWSTRS total scores, sustained at 12 w (-9.1 A/Abo vs. -4.9 PBO; $p = 0.019$). Investigator and pt VAS better for A/Abo vs. PBO. No difference between treatments in SF-36.	Open-label extension, dose could be increased or decreased from 250 U to 1000 U at investigator discretion
Truong et al., 2005	I	R, DB, PC	80	A/Abo 500 U or PBO	20 w	1-Change in total TWSTRS, baseline to 4 w 2-Change in pain VAS; pt-assessed signs/symptoms	A/Abo, 14%; PBO, 63% at w 4	Blurred vision and muscle weakness significantly greater in A/Abo vs. PBO ($p < 0.05$)	1-Mean change in TWSTRS 9.9 for A/Abo vs. 3.8 for PBO ($p = 0.01$). 2-Pain rating decreased significantly at 4 w and sustained through 8 w	
Poewe et al., 1998	I	R, DB, PC, prospective, dose ranging	75 BoNT-naive	A/Abo 250, 500, 1000 U or PBO	8 w, then blinding broken	1-Postural head deviation (Tsui scale), torticollis pain, dysphagia, need for retreatment at 8 w 2-Global improvement assessed by pt and physician, AEs, clinical global rating at 8 w	1	Most AEs mild and transient: neck weakness, voice change, dysphagia	1-Clinically meaningful reduction in postural head deviation in all active treatment groups; 50%% of 200 U and 500 U groups, 39% of 1000 U group requested retreatment at 8 w, vs. 94% in PBO group. 2-Optimal responses in 13/18 pts in 1000 U, 7/16 in 500 U, 7/19 in 250 group, 2/20 in PBO.	Clinically effective dose range deemed 250–1000 U
Botox [Package insert], 2010	I	R, DB, PC	170	A/Ona mean dose 236 U or PBO	≥10 w	1-Change in CDSS at 6 w; increased % of pts with improvement on PGAS at 6 w 2-Pain frequency and severity	NA	Safety data pooled with other controlled and uncontrolled studies; specific data from this trial NA	1-Positive for change in CDSS ($p < 0.05$) and improvement on PGAS with A/Ona (A/Ona, 51%; PBO, 31%). 2-Numeric improvements on pain frequency and severity scales with A/Ona vs. PBO.	Both components of primary had to be positive

(*continued on next page*)

Table 4 (*continued*)

Ref	AAN class	Design	*N*	Treatment (serotype/brand/dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Brashear et al., 1999	I	R, DB, PC	109	B/Rima 5000 U, 10,000 U or PBO	16 w	1-TWSTRS Total score at 4 w 2-Physician & pt Global Assessment of Change at 4 w 3-Pt Analog Pain Assessment at 4 w	4	Most AEs mild; most common: neck pain secondary to CD (30), dry mouth (15), dysphagia (13), headache (17)	1-Mean TWSTRS Total score improvement: 9.3 for 5000 U, 11.7 for 10,000 U B/Rima vs. 4.3 for PBO ($p < 0.004$). 2-Pt and PGAS significant for 10,000 U ($p = 0.004$) and 5000 U ($p = 0.001$). 3-Pt Analog Pain Assessment better with 10,000 and 5000 U B/Rima vs. PBO ($p = 0.0002$; $p = 0.001$).	
Brin et al., 1999	I	R, DB, PC	77 BoNT/A nonresponders	B/Rima 10,000 U or PBO	16 w	1-Total TWSTRS at 4 w 2-Pt Global Assessment of Change at 4 w Others: TWSTRS severity, disability, and pain subscales at 8 and 12 w; global scores at 4 w	1 PBO	Dry mouth: 44% B/Rima, 3% PBO; dysphagia: 28% B/Rima, 5% PBO	TWSTRS Total scores: significant improvement at 4 and 8 w ($p \leq 0.01$). 2-Pt Global Assessment of Change: 39.5 PBO vs. 60.2 B/Rima ($p = 0.0001$).	
Lew et al., 1997	I	R, DB, PC	122	B/Rima 2500, 5000, 10,000 U, or PBO	16 w	1-TWSTRS Total Score vs. baseline at 4 w 2-TWSTRS Severity, Disability, Pain subscales at 4 w; SIP, Analog Pain Assessment	0	Most AEs mild-moderate: dry mouth 14 B/Rima vs. 1 PBO; dysphagia 16 vs. 0; infection 13 vs. 0.	Improvement in all active groups at 4 w vs. baseline: 11.6, 12.5, 16.4 vs. 3.3 PBO ($p = 0.0001$); Severity: 3.5, 4.5, 4.7 vs. 1.6 PBO ($p = 0.003$). Disability: 3.8, 3.6, 5.4 vs. 0.7 PBO ($p = 0.002$). Pain: 4.4, 4.3, 6.4 vs. 1.0 PBO ($p = 0.0004$). SIP = NS.	
Comella et al., 2011	I	R, DB, PC	233	A/Inco 120 U, 240 U, or PBO	20 w or need for reinjection	1-Change in TWSTRS total score baseline–4 w postinjection 2-Change in TWISTRS Motor Severity, Disability subscales 4 w, 8 w, final visit; change in total TWISTRS score at 8 w, final visit	3 A/Inco due to AEs	AEs in 57%, 55%, 50% of A/Inco 120 U, 240 U, PBO; dysphagia, neck pain, muscle weakness more common with A/Inco vs. PBO; 4 SAEs in 240 U group, unrelated to study drug	1-Significant improvement in both active groups vs. PBO ($p < 0.001$). 2-Significant improvement in both active groups vs. PBO ($p < 0.02$).	120 U dose/treatment recommended in the Xeomin PI; higher dose did not provide additional efficacy, associated with increased AEs
Comparative: active comparator or multiple doses										
Odergren et al., 1998	I	R, DB, active comparator	73	A/Abo 477 U, A/Ona 152 U	12 w	1-Tsui score at 12 w or retreatment if sooner; time to retreatment 2-Change in Tsui score; investigator's global assessment	0	AEs similar in both groups, mostly mild to moderate; severe AEs in 5% of A/Abo and 2% of A/Ona pts; drug-related: 32% in A/Abo, 26% in A/Ona. Most common at 1–4 w: dysphagia, pharyngitis	1-No difference between treatments in Tsui score or time to retreatment. 2-More A/Abo pts had >50% improvement but response profiles were similar.	Two primary end points; clear analysis plan

Brans et al., 1996	I	R, DB, parallel, prospective	66	A/Abo 292 MU vs. trihexyphenidyl 262 MU	12 w	1-Difference between groups on TWISTRS Disability Scale 2-Improvement ≥3 points on TWISTRS Disability, Tsui scales; changes on Pain scale, General Health Perception Subscale of Dutch MOS QoL Scale	4	More AEs in trihexyphenidyl ($p < 0.0001$): dry mouth, forgetfulness, fatigue; 3 A/Abo pts with neck weakness	1-More A/Abo pts improved (43%) vs. trihexyphenidyl pts (19%; $p = 0.0097$). 2-On Tsui scale, more A/Abo pts improved (72%) vs. trihexyphenidyl pts (38%).
Benecke et al., 2005	I	R, DB, parallel active, noninferiority	463	140 U A/Inco or 201 U A/Ona	16 w	1-Change in TWSTRS Severity subscale at 4 w 2-TWSTRS Severity at final visit; TWS Pain, VAS Pain, Global Response Scale; responder rates, investigators global assessment	18 A/Inco, 25 A/Ona	0 treatment-related SAEs; AEs: 28.1% A/Inco, 24.1% A/Ona; dysphagia most frequent AE	1-Change in TWSTRS Severity score −6.6 points A/Inco vs. −6.4 points A/Ona; met noninferiority. 2-No differences between groups in secondary end points.
Pappert et al., 2008	I	R, DB, active comparator, noninferiority	111	A/Ona 150 U or B/Rima 10,000 U	4 w	1-TWSTRS total score at 4 w 2-TWSTRS subscores, Subject Pain VAS, Subject and PI Global VAS at 4 w	3/group	No significant differences in moderate or severe AEs; dry mouth more frequent in B/Rima (39.3% vs. 7.3%; $p = 0.0001$)	1-Noninferiority met. 2-Similar effects of both treatments on all secondary variables, including duration of effect (median, 13.1 and 13.7 in A/Ona and B/Rima arms).
Comella et al., 2005	I	R, DB, parallel	139	A/Ona max dose 250 U; B/Rima max dose 10,000 U	20 w or until loss of 80% of clinical effect	1-Change in total TWSTRS at 4 w 2-TWSTRS subscales for Motor Severity, Pain, ADLs; PGAS, SGA at 4 w	10/74 (A/Ona) vs. 3/65 (B/Rima)	Dysphagia and dry mouth more frequent with B/Rima ($p < 0.0001$); 5 SAEs not related to treatment	1-No significant differences in efficacy, duration of effect. Modestly longer duration of benefit for A/Ona (14 vs. 12.1 w; $p = 0.033$) in pts with clinical response at 4 w.

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; ADL, activities of daily living; AE, adverse event; A/Inco, incobotulinumtoxinA; A/Ona, onabotulinumtoxinA; BoNT, botulinum neurotoxin; B/Rima, rimabotulinumtoxinB; CD, cervical dystonia; CDSS, Cervical Dystonia Severity Scale; DB, double blind; D/C, discontinuations; MOS, medical outcome study; MU, mouse units; NNH, number needed to help; PBO, placebo; PC, placebo-controlled; PGAS, Physician Global Assessment Scale; PI, principal investigator; R, randomized; SAE, serious adverse event; SF-36, Short Form Health Survey; SGA, subjective global assessment; SIP, Sickness Impact Profile; Tsui, Tsui rating scale for cervical dystonia; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; VAS, visual analog scale.

previously treated with A/Ona and those not previously treated. A/Inco was generally well tolerated, with only three premature discontinuations in the active-treatment arms due to AEs.

Class I active-comparator studies showed that B/Rima (Pappert et al., 2008) and A/Inco (Benecke et al., 2005) were noninferior to A/Ona according to the prespecified margins. Two comparator studies (both Class I) showed no significant difference in efficacy between BoNT-A and BoNT-B (Comella et al., 2005; Pappert et al., 2008). Dry mouth was reported more frequently in the B/Rima group compared with the A/Ona group in both studies (Comella et al., 2005; Pappert et al., 2008).

In a Class II study, one of two head-to-head comparisons of A/Ona and A/Abo with dosing ratios of 3 U or 4 U A/Abo to 1 U A/Ona, in a crossover design, both A/Abo doses reduced the Tsui and TWSTRS scores more than A/Ona at 1 month postinjection (Ranoux et al., 2002). In addition, the duration of effect was reported to be longer for the 1:4 A/Abo dose regimen compared with A/Ona (mean 114 days vs. 89.3 days for A/Abo and A/Ona, respectively). Mean doses for the three treatments were not provided by the authors. An apparent greater clinical efficacy of A/Abo was accompanied by a greater frequency of AEs: a higher percentage of patients reported AEs with A/Abo 1:4 (36.0%) vs. A/Ona (17.6%). The most common AE was dysphagia, in 3.0% of A/Ona compared with 15.6% and 17.3% (A/Abo 1:3 and 1:4 dose ratios, respectively). In contrast, one Class I study (Odergren et al., 1998) compared A/Abo to A/Ona using a 3:1 dosing ratio (mean doses, 477 U A/Abo and 152 U A/Ona) and noted no difference between treatments in the change in Tsui score or duration of action.

A Class I study comparing A/Abo to trihexyphenidyl in 66 patients naïve to BoNT therapy showed greater improvement on both the TWSTRS and Tsui scales with A/Abo, with fewer AEs compared with trihexyphenidyl (Brans et al., 1996).

3.4.1. Summary

The published evidence supports Level A recommendations for all four BoNT formulations for the treatment of CD.

3.4.2. Evidence gaps and recommendations for future studies

Further controlled comparisons of dosing regimens for each formulation would provide quality evidence to support the existing empirically based dosing recommendations. Although there is head-to-head comparison data on A/Ona vs. A/Inco and vs. B/Rima, there is a need for controlled, randomized comparison of A/Ona vs. A/Abo.

3.5. Limb dystonia

The use of BoNT for limb dystonia is supported by one Class I (Kruisdijk et al., 2007) and one Class II study (Contarino et al., 2007) of A/Abo and three Class II studies of A/Ona (Cole et al., 1995; Tsui et al., 1993; Yoshimura et al., 1992a) with a total of 116 patients (see Table 5). All of these studies were randomized, double-blind, and controlled and ranged from 2 weeks to 3 months in duration. Outcome measures included handwriting analysis (speed, accuracy) and subjective ratings. The most frequent AE in all studies was focal weakness, which occurred more commonly with BoNT treatment than placebo. All studies except one noted significantly greater improvement in objective outcomes. In one study, based on blinded rating, handwriting improved after 59% of A/Ona treatments vs. 38% of placebo injections (Yoshimura et al., 1992a); partly due to a small sample size ($N = 17$), however, this difference was not statistically significant. A Class II methodologic study of patients treated with A/Ona injections for dystonic writer's cramp demonstrated that 30-min exercise during the immediate postinjection period increased grip weakness, with no significant effect on subjective benefit (Chen et al., 1999). Two class II methodologic studies compared EMG vs. muscle stimulation for needle localization; one of these studies showed enhanced accuracy of needle placement under EMG guidance (Molloy et al., 2002), while the other was inconclusive (Geenen et al., 1996).

3.5.1. Summary

The available evidence supports Level B recommendations for both A/Abo (based on one Class I (Kruisdijk et al., 2007) and one Class II (Contarino et al., 2007) study) and A/Ona (two Class II studies) (Tsui et al., 1993; Yoshimura et al., 1992a). No published studies were identified for A/Inco or B/Rima, which results in a Level U recommendation for these two formulations.

3.5.2. Evidence gaps and recommendations for future studies

Further studies are needed to provide Level A recommendations for all BoNT formulations and to establish optimal dosing regimens. However, given the complexity of the hand and the variability of patients, each patient will have to be individually considered for dose optimization.

3.6. Laryngeal dystonia

Despite long-standing use of BoNT for this disorder, there is only one high-quality controlled, Class I study confirming the efficacy and safety of A/Ona, in 13 patients with adductor spasmodic dysphonia (ADSD; see Table 6) (Troung et al., 1991). Follow-up outcome assessments at 4 days postinjection, which included acoustic frequency range and patient ratings, were improved in the active treatment but not the placebo group.

Lower-quality evidence is available from a number of Class III studies that compared two methods of BoNT administration (Adams et al., 1995; Finnegan et al., 1999; Ludlow et al., 1988; Wong et al., 1995). A single Class III study evaluated B/Rima in 13 patients with ADSD who received total doses ranging from 50 to 200 U and showed efficacy on blinded voice ratings (Adler et al., 2004). One study assessed the effect of A/Ona in 15 patients with abductor spasmodic dysphonia (Bielamowicz et al., 2001). In this Class III prospective crossover trial with blinded speech evaluation, patients perceived benefit that was not substantiated by blinded counts of symptom frequency.

3.6.1. Summary

Available evidence supports a level C recommendation for the use of A/Ona as treatment of adductor laryngeal

Table 5
Limb dystonia.

Ref	AAN class	Design	*N*	Treatment (serotype/brand// dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo-controlled										
Kruisdijk et al., 2007	I	R, DB, PC	40 (writer's cramp)	A/Abo 20 MU or PBO; mean total dose, first and second treatments, 178 MU	1 y	1-Pt wish to continue treatment 2-VAS, Symptom Severity Scale, Functional Status Scale, WCRS, Writing Speed	0	Hand weakness in 12 A/Abo; injection pain in 1 A/Abo and 3 PBO pts	1–70% A/Abo vs. 32% PBO pts wanted to continue treatment ($p = 0.03$). 2-Significant improvement with A/Abo in all secondary outcomes except Functional Status Scale.	
Contarino et al., 2007	II	R, DB, PC, P	39 (29 writer's cramp, 10 control)	A/Abo 20 MU or PBO; total dose, first and second treatments, 178 MU	8 w	Change in writing speed at 8 w	2	Not reported	A/Abo showed significantly greater improvement in number of lines written in 2 min: 2.1 lines in A/Abo group vs. 0.3 lines in PBO ($p = 0.007$).	No mention of safety and tolerability
Yoshimura et al., 1992b	II	R, DB, PC, P	17 (10 occupational, 3 idiopathic, 2 poststroke, 2 PD)	A/Ona 3–120 U or PBO	4 mo	1-Difference in response between A/Ona and PBO by subjective pt rating, blinded videotape review, handwriting analysis	1	Focal weakness in 53% of A/Ona injections, more common with higher dose; muscle stiffness, pain, malaise, muscle twitching, paresthesia, nausea	No significant change in blinded rating (59% A/Ona, 38% PBO). Subjective rating improved in 14 A/Ona pts vs. 1 PBO pt.	
Tsui et al., 1993	II	R, DB, PC	20 (writer's cramp)	A/Ona 25–30 U/muscle or PBO	3 mo	Writing speed, accuracy, performance on Gibson's maze, copying, pt subjective assessment	N/A	Pen control worse for 8 d in 1 pt injected with A/Ona	Speed, accuracy, performance on Gibson maze significantly improved in A/Ona group; pain decreased in A/Ona group.	Objective outcome measures; wrist posture distortion most helpful in predicting outcome
Cole et al., 1995	II	R, DB, PC	10	A/Ona 5–30 U or PBO	3–4 mo	Dystonia, ease of writing, performance skill; pt subjective rating of response, manual muscle testing, physician rating of videotapes	N/A	Not reported	Subjective: 9/10 pts had at least moderate improvement. Objective: 6 A/Ona pts improved, 1 PBO pt improved.	

(*continued on next page*)

Table 5 (*continued*)

Ref	AAN class	Design	*N*	Treatment (serotype/brand// dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Methodologic										
Chen et al., 1999	II	R, SB, cross-over comparison of rest vs. writing	8 Writer's cramp	A/Ona 2.5–25 U	3 mo	Objective strength testing; self-reported rating of wrist flexion strength, wrist extension, WCRS, blinded evaluation of videotapes and writing samples	1	Nor reported	Exercise after injection decreased grip strength but did not affect subjective benefit.	
Geenen et al., 1996	II	R, SB	12 Focal hand dystonia	A/Ona 25 U (10 U in 1 pt) Stimulation vs. EMG recording for needle localization	3 w	1-Effects on target muscle 2-Effects on other muscles Methods of localizing target muscles for injection	N/A	Not reported	No difference in target muscle weakness in 4/8 in EMG group, 1/4 in stimulation group. Other muscles weakened in 5/7 pts.	Not powered to test difference in techniques
Molloy et al., 2002	II	R, SB	14 Focal hand dystonia	EMG vs. no EMG for needle localization	N/A	% of muscle insertions correctly placed in selected muscle without EMG guidance	0	Not reported	Correct muscle identified without EMG in 37% of needle placements ($p < 0.001$).	Conclusion: EMG guidance is needed for correct localization of desired muscles, regardless of physician level of skill.

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; AE, adverse event; A/Ona, onabotulinumtoxinA; B, blinded; DB, double blind; D/C, discontinuations; EMG, electromyography; MU, mouse units; P, prospective; PBO, placebo; PC, placebo-controlled; PD, Parkinson's disease; R, randomized; SB, single blind; VAS, visual analog scale; WCRS, Writer's Cramp Rating Scale.

Table 6
Laryngeal dystonia.

Ref	AAN class	Design	*N*	Treatment (serotype/ brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo controlled										
Troung et al., 1991	I	R, DB, PC	13 ADSD	A/Ona 5 MU or PBO/ thyroarytenoid muscle	4 d	1-Fundamental frequency, phonation times, fundamental frequency range, perturbation, spectrographic analysis 2-Pt ratings and physician rating of videotape recordings	0	Excessive breathiness (2), mild bleeding (1) in A/Ona pts; vocal fold edema (1) in PBO	1-Improved fundamental frequency range ($p < 0.01$), perturbation ($p = 0.05$), spectrographic analysis ($p < 0.05$) in A/Ona group. 2-Pt ratings improved in A/Ona group vs. PBO ($p < 0.01$).	
Methodologic and uncontrolled										
Bielamowicz et al., 2001	III	P, R cross-over, blinded evaluation of speech	15 ABSD	A/Ona 5 U/side 2 weeks apart, crossover from endoscopic and percutaneous injections; second series at >6 mo	6 mo	1-Blinded counts of symptom frequency 2-Pt ratings of improvement	4 not treated by endoscopic technique due to discomfort	Stridor in 1 pt; unilateral abduction impairment in 47% and residual unilateral abductor impairment in 35% after second percutaneous injection	11 pts reported benefit not seen in speech pathologist blinded assessments. No difference in breathy breaks. No significant symptom benefit for either technique in ABSD.	
Bielamowicz and Ludlow, 2000	III	SB, uncontrolled	10 ADSD	A/Ona 15–87 U	12–39 d	1-Overpressure, tremor, voice quality roughness; voice breaks 2-EMG: maximum muscle activation, number of muscle bursts, % maximum during speech	0	None reported	Improved speech symptom ($p = 0.005$) and EMG ($p = 0.009$) ratings. Changes in number of muscle and speech breaks were related ($p \leq 0.05$).	
Warrick et al., 2000	III	Open-label, examiner blinded, cross-over	10 Essential voice tremor	A/Ona unilateral arm 15 U, bilateral arm 2.5 U; technique switched at later injection	16 w after each injection	1-Max phonation time; aerodynamics: oral airflow, intraoral pressure, sound pressure 2-Pt perception: VAS overall satisfaction, voice improvement, tremor reduction, swallowing, wish to continue, improvement with bilateral vs. unilateral	1	Breathiness, coughing, choking, swallowing problems similar in both arms	Similar results in unilateral and bilateral arms. 3 patients had reduced tremor with bilateral and 2 with unilateral injections; majority of pts experienced subjective reduction in vocal effort.	8 pts requested re-injection at end of study
Finnegan et al., 1999	III	Cross-over, controlled study of two methods	5 ADSD (10 controls from earlier research)	A/Ona 5 U thyroarytenoid only, PBO in thyrohyoid and sternothyroid vs. 5 U thyroarytenoid, 7.5 U sternothyroid, 7.5 U thyrohyoid	4–12 mo	1-Changes in airflow and intraoral pressure 2-Coefficient of variation of airflow	0	None Reported	Mean airflow and stability of airflow increased with A/Ona injection in laryngeal muscles. Changes in coefficient of variation inversely related to airflow.	No difference between treatments, possibly underpowered

(*continued on next page*)

Table 6 (*continued*)

Ref	AAN class	Design	*N*	Treatment (serotype/ brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Adams et al., 1995	III	R, blinded	50 ADSD	A/Ona 15 unilateral or 2.5 U bilateral injections	2–6 w	1-Maximum phonation time 2-Average fundamental frequency, standard deviation of fundamental frequency, jitter, shimmer, signal/ noise ratio; perceptual judgments of voice	0	Longer duration of excessive phonatory airflow after bilateral injections; higher breathiness ratings in both groups at 2 w	At 2 w, no significant differences between groups. At 6 w, only difference was in maximum phonation time (lower in bilateral group; $p < 0.05$). At 2 w and 6 w, unilateral and bilateral groups showed equivalent improvement.	No difference
Wong et al., 1995	III	R, controlled, unblinded, parallel groups	20 ADSD	A/Ona 2.5 U/ thyroarytenoid muscle; vocalization vs. nonvocalization for 30 m postinjection	10 w	1-Acoustic spasm severity 2-Maximum phonation time, variance in fundamental frequency 3-Aerodynamics	0		1-Vocal rest after A/Abo produced superior and longer-lasting spasm severity ($p < 0.05$). Significant greater reduction in spasm severity at 2 and 10 w in nonvocalizing pts. 2-Vocal rest after A/Abo produced superior and longer-lasting maximum phonation time. 3-No aerodynamics benefits with nonvocalization.	Longer-lasting benefits in vocal rest group
Ludlow et al., 1988	III	Uncontrolled, blinded, quantitative assessment	16 ADSD	A/Ona 15–60 U unilateral injection	4 mo after last injection	1-Pitch and voice breaks, phonatory aperiodicity, sentence time; decrease in vocal fold movement	0	14 reduced voice volume, 13 reduced swallowing speed, 1 aspiration	Significant reductions in pitch and voice breaks, phonatory aperiodicity, sentence time when injections resulted in vocal fold paralysis.	Uncontrolled study
Adler et al., 2004	III	Open-label, SB, dose-finding	13 ADSD	B/Rima 25–200 U	8 w	1-Pts rating of change in effort to speak, symptom severity, breathiness, difficulty swallowing, AEs 2-Blinded ratings of voice	0	Hypophonia and breathiness (4) at 1 w improved by 4 w; vocal fold soreness (3)	1-Pts rating, 200 U at 8 w, spasms improved in 8/10 ($p < 0.001$); disease severity improved. 2-Blinded rating of voice improved 44% (1 w)-24% (8w) in 200 U group; 50 U showed substantial improvement at 1 w and 4 w.	

A/Abo, abobotulinumtoxinA; AAN, American Academy of Neurology; ABSD, abductor spasmodic dysphonia; ADSD, adductor spasmodic dysphonia; AE, adverse event; A/Ona, onabotulinumtoxinA; B/Rima, rimabotulinumtoxinB; DB, double blind; D/C, discontinuations; EMG, electromyography; MU, mouse units; P, prospective; PBO, placebo; PC, placebo-controlled; R, randomized; SB, single blind; VAS, visual analog scale.

dystonia, based on a single Class I study (Troung et al., 1991) and a number of Class III studies (Adams et al., 1995; Adler et al., 2004; Bielamowicz and Ludlow, 2000; Bielamowicz et al., 2001; Finnegan et al., 1999; Ludlow et al., 1988; Warrick et al., 2000; Wong et al., 1995). Level U recommendations are warranted for B/Rima (insufficient data) as well as for A/Abo and A/Inco (no published studies identified.)

3.6.2. Evidence gaps and recommendations for future studies

Further studies are needed to determine the appropriate recommendations for all BoNT formulations and to establish optimal dosing regimens. There is also a need to objectively assess the effects of BoNT treatment in patients with the abductor form of spasmodic dysphonia.

3.7. Tics

Two studies evaluated the effect of A/Ona, with a total of 55 patients with tic disorders: a Class II placebo-controlled crossover study of 20 patients with simple tic disorders (Marras et al., 2001) and an uncontrolled study of 30 patients with Tourette syndrome. Both studies showed benefits related to BoNT treatment (see Table 7). The Class II study showed a 39% reduction in tic number and a reduction in tic urge score (Marras et al., 2001), and the open-label study showed an improvement in tics (mean peak effect of 2.8 on a scale of 0–4), with a 14.4-week total duration of benefit (Kwak et al., 2000). Although there is a lack of controlled trials, several case series documented that focal chemodenervation with BoNT ameliorates not only the involuntary movements but also the premonitory sensory component of motor and phonic tics and may be particularly useful in potentially life threatening "whiplash" neck tics (Aguirregomozcorta et al., 2008; Cheung et al., 2007).

3.7.1. Summary

Although BoNT does appear to improve focal tics, such as blinking and dystonic tics involving the neck and shoulders, because of lack of Class I studies, the treatment may be considered only in selected cases. A Level U recommendation is warranted at this time for all four formulations.

3.7.2. Evidence gaps and recommendations for future studies

There is a need for quality trials of the three BoNT formulations that have not been evaluated to date and at least one more confirmatory trial of A/Ona.

3.8. Tremor

Three Class II studies evaluated the treatment of tremor with A/Ona: two studies in patients with essential hand tremor and one study in patients with head tremor (see Table 8). All studies were positive, with modest improvement (1–1.5 points on a scale of 0–4) for hand tremor (Brin et al., 2001; Jankovic et al., 1996) and twice the number of patients reporting subjective and objective benefit after A/Ona compared with placebo treatment for head tremor in a crossover study (Pahwa et al., 1995).

Table 7
Tics.

Ref	AAN class	Design	N	Treatment (serotype/brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Marras et al., 2001	II	R, PC, crossover	18 motor tics	A/Ona (dose not specified)	12 w, then every 4 w until return to baseline	1-Number of treated tics at w 2 vs. baseline 2-Frequency, change in Shapiro Tourette Symptom Severity Scale, urge to perform, premonitory sensation, pt global assessment of change	2 during active phase	12 pts had muscle weakness with A/Ona on physical exam not evident on videotape ratings	1–39% decrease with A/Ona vs. 6% increase with PBO ($p < 0.01$). 2-0.46 reduction in urge score with A/Ona vs. 0.49 increase with PBO ($p = 0.02$); no change in other secondary measures.	Doses not specified
Kwak et al., 2000	IV	Uncontrolled	35 Tourette syndrome	A/Ona total mean dose 502 U	21 mo	1-Peak effect, global rating, latency, total and maximum duration	N/A	Neck weakness (4), dysphagia (2), ptosis (2), all mild and transient	Mean peak response, 2.8; mean duration of maximum benefit, 12.3 w; total duration, 14.4 w; latency to onset of effect, 3.8 d. 21/25 (84%) with notable premonitory sensory symptoms derived marked symptom relief.	

AAN, American Academy of Neurology; A/Ona, onabotulinumtoxinA; D/C, discontinuations; PBO, placebo; PC, placebo-controlled; R, randomized.

Table 8
Tremor.

Ref	AAN class	Design	*N*	Treatment (serotype/brand//dose)	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Brin et al., 2001	II	R, DB, PC parallel group	133 essential hand tremor	A/Ona 50 U, 100 U, or PBO	16 w	Tremor severity, tremor treatment response, motor tasks, functional ability, QoL, grip strength	0	Hand weakness in 30% of low-dose, 70% of high-dose group	Significant difference for low- and high-dose groups in postural tremor severity at 6, 12, 16 w; kinetic tremor significant only at 6 w. Peak improvement of 1.3–1.5 in tremor at 16 w ($p < 0.0001$).	A single treatment using rigid protocol does not reflect clinical practice
Jankovic et al., 1996	II	R, DB, PC	25 essential hand tremor	A/Ona 50 U; if no response, 100 U at 4 w	4 m	Tremor rating; functional severity, peak effect of drug, global assessment by pt and examiner SIP, accelerometry	1 in PBO due to pregnancy	Mild (50%) or moderate (42%) finger weakness in 11 A/Ona pts	No statistical difference on total UTRA score, though tremor improved 1grade in 91.7%, 2 grades or more in 75% of pts. Postural tremor, treatment response, peak effect favored A/Ona ($p \leq 0.05$) at 4 w.	Improvement in clinical but not functional ratings; does not reflect clinical practice
Pahwa et al., 1995	II	DB, PC crossover design	10 essential head tremor	A/Ona 200 U or PBO	8 w	Improvement on subjective and clinical rating scales at 2, 4, 8 w	0	Mild neck weakness, resolved spontaneously	No significant differences in subjective and clinical ratings between groups. 8 treated pts vs. 4 PBO pts reported improvement.	Small sample; results not significant

AAN, American Academy of Neurology; A/Ona, onabotulinumtoxinA; DB, double blind; D/C, discontinuations; PBO, placebo; PC, placebo-controlled; QoL, quality of life; R, randomized; SIP, Sickness Impact Profile; UTRA, Unified Tremor Rating and Assessment.

3.8.1. Summary

Three Class II studies support a level B recommendation for the treatment of tremor with A/Ona: two studies in patients with essential hand tremor, and one study in patients with head tremor. No published studies were identified for A/Abo, A/Inco, or B/Rima, warranting a Level U recommendation for these three formulations.

3.8.2. Evidence gaps and recommendations for future studies

Further clinical trials are needed to evaluate the efficacy and tolerability of A/Abo, A/Inco, and B/Rima for this movement disorder, as well as trials comparing BoNT to other therapies. At least one Class I study should be performed in patients with essential hand tremor without injecting the wrist extensors, as chemodenervation of the latter was associated with extensor finger weakness.

Conflicts of interest

Mark Hallett has received funding from the Neurotoxin Institute.

Alberto Albanese serves on the editorial board of the European Journal of Neurology (Associate editor) and Frontiers in Movement Disorders (Editor in Chief). He has also received speaker's honoraria from Merz and Ipsen and a research grant from Allergan, and he has received royalties from publishing from Elsevier and Wiley–Blackwell.

Dirk Dressler has taken part in consultancies, studies, and projects and/or received grants and funding from the following companies: Allergen, Ipsen, Merz, Solstice, Syntoxin, UCB, Teva, Bayer, Desitin, Addex, and Abbott.

Karen Segal is currently employed by Mesoblast, Inc.

David Simpson has received consulting, research, and educational grants from Allergan, Merz, Ipsen, US Worldmeds Consulting, and Syntaxin.

Daniel Truong has served as a consultant for Merz Pharmaceuticals and Ipsen Pharmaceuticals, and as a Speaker for Ipsen Pharmaceuticals. He has received research funding from Allergan Pharmaceuticals, Merz Pharmaceuticals, and Ipsen Pharmaceuticals.

Joseph Jankovic has served as a consultant and received grants from Allergan Inc., Ipsen Limited, and Merz Pharmaceuticals.

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