Consensus Statement on the Use of Botulinum Neurotoxin to Treat Spasticity in Adults

NEUROTOXIN SPASTICITY CONSENSUS GROUP:
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INTRODUCTION

Spasticity is characterized by increased muscle tone, exaggerated tendon jerks, and poor control of voluntary movement that occurs as part of an upper motor neuron syndrome. Patients with spasticity are at high risk of sustaining rheologic changes to the involved muscles, ultimately leading to contractures and painful limb deformities. The principal goal of spasticity management is to prevent irreversible soft-tissue changes and tendon contractures by maintaining muscle length and normal limb positioning.

Treatment options ranging from conservative to aggressive measures, including physical and occupational therapies; oral and intrathecal medications; surgery; and focal chemical denervation with phenol, alcohol, and botulinum neurotoxin (BoNT). Therapy is dictated by the duration, distribution, and severity of disease. Management of spasticity is driven by patient needs and long-term functional goals (Figure 1, page 672).

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BoNT exists as seven immunologically distinct serotypes—A, B, C1, D, E, F, and G. These serotypes are produced by the anaerobic, gram-positive, spore-forming bacterium Clostridium botulinum. Three principal clinical formulations of BoNT are in use worldwide:

- two BoNT-A formulations: Botox (Allergan, Inc.) and Dysport (Ipsen, Ltd.)
- a BoNT-B formulation, Myobloc/Neurobloc (Solstice Neurosciences, Inc.)

Of these, Botox and Myobloc have been approved by the Food and Drug Administration (FDA) for clinical use in the U.S., although neither agent is indicated for the treatment of spasticity. These formulations are unique and should not be considered generic equivalents or interchangeable, because they differ in manufacturing, units of activity, and clinical potency.

Clinical use of BoNT is administered intramuscularly. It reduces neuromuscular transmission by modulating the release of acetylcholine and other vesicular neuropeptides from nerve terminals. It is safe and effective in the treatment of various conditions characterized by muscle overactivity such as cervical dystonia. Its safety and efficacy in the treatment of adult focal spasticity are discussed in this evidenced-based review.

REVIEW PROCESS

The authors of this article—academic-affiliated neurologists and physiatrists with experience in the use of neurotoxins for spasticity, pain, headache, and other conditions—were recruited by a health care consultant under a grant from Allergan. Most of us met twice in person to review the evidence and to arrive at a consensus. Several telephone conferences and electronic communications aided the development of our Consensus Statement (see page 674).

We conducted a literature search using Ovid Medline and PubMed to identify clinical trials involving adults with spasticity that were published between 1965 and May 2005 (Table 1). Our findings revealed 570 articles on spasticity and BoNT; 17 of these satisfied the a priori selection criteria for rigorous study design (Table 2).

Most of the trials used BoNT-As (Botox and Dysport); only one study involved BoNT-B (Myobloc). Our Consensus Group decided to review nine studies using BoNT available for clinical use in the U.S. (Botox and Myobloc). These studies involved 400 adults with spasticity from a number of causes, such as stroke, head injury, and multiple sclerosis (MS). Based on the
Oxford Centre for Evidence-Based Medicine (OCEBM) criteria (Tables 3 and 4), six of the reviewed studies were rated “Level 1b” and three were rated “Level 1b-minus” (Table 5).6

**LITERATURE REVIEW**

**The Snow Study**

Using a randomized, double-blind, placebo-controlled, crossover study design, Snow et al. (1990) evaluated the safety and efficacy of BoNT-A in the treatment of lower-limb spasticity secondary to MS. Nine patients received injections of saline or BoNT-A (total dose: 400 units, diluted at 100 units/ml), divided among the leg adductors (adductor brevis, longus, and magnus). Patients were evaluated at two and six weeks after treatment. All patients were then crossed over and given repeated injections of either BoNT-A or saline after three months. The patients were re-evaluated at two and six weeks.

At week six, BoNT-A produced a significant reduction in spasticity scores (the sum of the Ashworth Scale [range, 0–5] and in the Spasm Frequency Score [range, 0–4]) (mean, 7.9 ± 4.87 to 4.7 ± 4.31; \( P = .009 \)).

BoNT-A also significantly reduced caregiver burden (\( P = .009 \)) and hygiene scores (\( P = .02 \)), whereas placebo did not.

No adverse drug events (ADEs) were reported in this trial (Level 1b evidence).

**The Grazko Study**

Grazko et al. (1995) evaluated BoNT-A in the treatment of spasticity using a randomized, double-blind, placebo-controlled, crossover study design. Eleven patients received injections of saline or BoNT-A (total dose: 400 units, diluted at 100 units/ml), divided among the leg adductors (adductor brevis, longus, and magnus). Patients were evaluated at two and six weeks after treatment. All patients were then crossed over and given repeated injections of either BoNT-A or saline after three months. The patients were re-evaluated at two and six weeks.

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**TABLE 2  Results of Search Strategy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity citations (studies), all toxin types</td>
<td>570</td>
</tr>
<tr>
<td>Citations meeting all criteria</td>
<td>17</td>
</tr>
<tr>
<td>Spasticity citations for BoNT-A (Botox)</td>
<td>8</td>
</tr>
<tr>
<td>Spasticity citations for BoNT-A (Dysport)</td>
<td>8</td>
</tr>
<tr>
<td>Spasticity citations for BoNT-B (Myobloc)</td>
<td>1</td>
</tr>
<tr>
<td>Citations reviewed</td>
<td>9*</td>
</tr>
</tbody>
</table>

* Only citations involving FDA-approved botulinum neurotoxins for clinical use. Botox and Myobloc were reviewed.

BoNT-A = botulinum neurotoxin type A; BoNT-B = botulinum neurotoxin type B.
crossover design. In 12 patients with upper- or lower-limb spasticity caused by stroke, MS, traumatic brain injury, or perinatal hypoxia, 25 to 290 units of BoNT-A or saline was injected into the involved muscles. The injections were directed by “surface [anatomic] landmarks for motor points.” The mean dose was 138 units, and the concentration varied according to muscle size.

Patients were evaluated at two weeks after treatment, and the crossover injection was given at the return of baseline muscle tone. All patients achieved at least a two-point reduction in Ashworth Scale scores as well as marked improvements in subjectivity (ease of movement and posture) and nursing care. Patients with painful spasms reported a reduction in spasm frequency and intensity.

No placebo effect was observed in this trial. ADEs, such as injection-site pain, were generally mild and transient (Level 1b evidence).

**The Simpson Study**

Simpson et al. (1996) reported a randomized, double-blind, placebo-controlled, dose-ranging study of BoNT-A in the treatment of chronic upper-limb spasticity after stroke. Thirty-nine patients received injections of BoNT-A or matching placebo into the elbow and wrist flexors under electromyographic (EMG) guidance. The BoNT-A injections consisted of 75, 150, or 300 units, 3 ml in volume, with a concentration range of 25 to 100 units/ml. The patients were followed for 16 weeks.

The authors concluded that the group receiving 300 units of BoNT-A experienced statistically and clinically significant mean reductions in baseline wrist flexor tone at the second, fourth, and sixth weeks and in elbow flexor tone at the second and fourth weeks (BoNT-A vs. placebo, \( P \leq .05 \)), as measured on the Ashworth Scale. Both the 75- and 300-unit BoNT-A patient groups showed significant improvement in Physician and Patient Global

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**TABLE 3 Criteria for Levels of Evidence**

<table>
<thead>
<tr>
<th>Level*</th>
<th>Therapy/Prevention</th>
<th>Economic and Decision Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic review (with homogeneity†) of randomized, controlled trials</td>
<td>Systematic review (with homogeneity†) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual double-blinded randomized, controlled trial</td>
<td>Analysis based on: • Clinically sensible costs or alternatives • Systematic review(s) of the evidence, including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none</td>
<td>Absolute better-value or worse-value analyses‡</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review (with homogeneity†) of cohort studies</td>
<td>Systematic review (with homogeneity†) of Level &gt;2 economic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low-quality randomized, controlled trial§ and prospective open-label trial)</td>
<td>Analysis based on: • Clinically sensible costs or alternatives • Limited review(s) of the evidence or single studies, including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>Outcomes research</td>
<td>Audit or outcomes research</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity†) of case–control studies</td>
<td>Systematic review (with homogeneity†) of Level 3b and better studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case–control/retrospective studies</td>
<td>Analysis based on: • Limited alternatives or costs • Poor-quality estimates of data but including sensitivity analyses incorporating clinically sensible variations</td>
</tr>
<tr>
<td>4</td>
<td>Case studies/series</td>
<td>Analysis with no sensitivity analysis</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research, or “first principles”</td>
<td>Expert opinion without explicit critical appraisal or based on economic theory or “first principles”</td>
</tr>
</tbody>
</table>

* A minus is added to denote the level that fails to provide a conclusive answer because of lack of full methodology (e.g., randomization, blinding) reporting and subgroup analysis (potential introduction of bias).
† A systematic review is free of worrisome variations in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity are worrisome, and not all worrisome heterogeneity is statistically significant. Studies displaying worrisome heterogeneity should be tagged with a dash (“—”) after their designated level.
‡ Better-value treatments are clearly as effective as, but less costly or more effective than ( ), and equally or less costly than ( ).
Worse-value treatments are as effective as ( ) and more costly or less effective than ( ) and equally or more costly than ( ).
§ Low-quality, randomized, controlled trials refer to studies with inadequate randomization, blinding, or follow-up (below 80%).

Adapted from Oxford Centre for Evidence-Based Medicine. Available at: www.cebm.net.
Assessment Scale scores (–4 to +4, with 0 representing no change) at weeks four and six (BoNT-A vs. placebo, $P \leq .05$).

No consistent differences were observed between the groups for other outcome measures, including the Functional Independence Measure, the Rand 36-Item Health Survey 1.0, and the Fugl–Meyer Scale. Nonserious and reversible treatment-related ADEs were reported, including injection-site pain and finger twitching, although their frequency did not differ significantly between groups (Level 1b evidence).

**The Kirazli Study**

Kirazli et al. (1998) compared phenol with BoNT-A in the treatment of post-stroke spastic foot through a randomized, double-blind, parallel-group study. Twenty patients with ankle plantar flexion and foot-inversion spasticity received either 400 units of BoNT-A (50 units/ml under EMG guidance) or 3 ml of 5% phenol (i.e., tibial nerve block via nerve stimulation guidance). The patients were then followed for 12 weeks.

Both treatment groups experienced significant reductions in mean tone at baseline, although changes in Ashworth Scale scores for dorsiflexion and eversion were superior with BoNT-A therapy at weeks two and four (BoNT-A vs. phenol, $P < .05$). Unlike phenol, BoNT-A significantly improved walking velocity at all follow-up visits; like phenol, it significantly reduced EMG-measured duration of clonus throughout the trial.

Both treatment groups achieved comparable gains in active and passive range of motion, although Patient Global Assessment Scale scores were significantly improved with BoNT-A at all follow-up visits through the 12-week study period ($P < .05$) in the BoNT-A group at the second, fourth, and eighth weeks. No significant treatment-related ADEs were reported in the BoNT-A group, but 30% of the subjects in the phenol group developed dysesthesia that interrupted ambulation.

The study represented Level 1b-minus and was slightly downgraded because of differences in the baseline characteristics of the randomized subjects.

**The Richardson Study**

In 2000, Richardson et al. completed a 12-week, randomized, double-blind, placebo-controlled trial on the safety and efficacy of BoNT-A in the treatment of upper-limb and lower-limb spasticity secondary to stroke, traumatic brain injury, spinal cord injury, cerebral palsy, neoplasm, and hypoxia. Enrolled patients ($n = 52$) were stratified into upper-limb and lower-limb groups and were then randomly selected to receive a single treatment of BoNT-A (total dose: 30–500 units, diluted at 50 units/ml) or saline under EMG guidance. Outcome measures were assessed at baseline and at weeks three, six, nine, and 12. The investigators generated aggregate (overall) scores for each variable by summing the scores from each assessment.

Aggregate scores were significantly better in the BoNT-A group on the Modified Ashworth Scale ($P < .02$), in passive range of motion ($P < .03$), on the Rivermead Motor Assessment Scale (lower limb, $P < .05$), and in subjective ratings of problem severity ($P < .025$).

No significant between-group differences were found for other outcome measures, including the 10-meter Timed Walk Test ($P > .30$), the Rivermead Motor Assessment Scale (upper limb, $P > .15$), and the Modified Goal Attainment Scale. The only reported ADE was injection-site pain (Level 1b evidence).

**The Brashear Study**

In the largest controlled trial for BoNT-A in the treatment of spasticity, Brashear et al. (2002) randomly assigned 126 patients with upper-limb spasticity resulting from stroke to receive injections of placebo or BoNT-A (200–240 units) into the flexors of the wrist, fingers, and thumb (if involved). The concentration was not documented.

Subjects who received BoNT-A had superior improvement in flexor tone, in the wrist and fingers, according to Ashworth Scale scores, at all follow-up visits through the 12-week study period ($P < .001$ for all comparisons). At week six, 65% of patients in the BoNT-A group reported clinically meaningful functional improvement on the validated, four-point Disability Assessment Scale, compared with 27% of placebo subjects ($P < .001$).

Scores on the Physician and Patient/Caregiver Global Assessment Scales were significantly improved with BoNT-A at all follow-up visits through 12 weeks (BoNT-A vs. placebo, $P < .002$). The most frequently reported ADEs—incoordination, infection, and pain—did not differ significantly between groups (Level 1b evidence).

**The Brashear Study**

In a subsequent double-blind, randomized, placebo-controlled trial of post-stroke spasticity of the upper extremity by Brashear et al. (2004), 15 patients received injections of placebo or BoNT-B (total dose: 10,000 units; 5,000 units/ml) via electrical stimulation to confirm placement. The BoNT-B group achieved no statistically significant reductions in muscle tone, as measured by the Ashworth Scale, compared with placebo, in the elbow, wrist, or finger flexors over the 16-week study period, except in the wrist flexors at week two ($P = .03$).

There were no significant differences in scores between the groups in the Physician, Patient, or Therapist Global Assessment Scales. No significant improvements were observed in subjective pain, passive or active range of motion, or in functional measures, such as the Nine-Hole Peg Test or the Jebsen Test.
**TABLE 5  Level of Evidence Rating of Spasticity and Botulinum Neurotoxin Studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Level of Evidence</th>
<th>Study Details</th>
<th>Spasticity Diagnosis/Etiology</th>
<th>Dose Details</th>
<th>Injection Site</th>
<th>Outcome Measures/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snow et al. (1990)7</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled, crossover</td>
<td>Lower limb</td>
<td>400 units of BoNT-A</td>
<td>Hip adductors</td>
<td>(+) Spasticity score = ASH x spasm frequency: week 6</td>
</tr>
<tr>
<td>Grazko et al. (1995)8</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled, crossover</td>
<td>Lower limb, upper limb</td>
<td>25–290 units of BoNT-A</td>
<td>Muscles of the upper and lower limbs</td>
<td>(+) ASH: 2-grade improvement in all patients with spasticity</td>
</tr>
<tr>
<td>Simpson et al. (1996)9</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled, dose-ranging</td>
<td>Upper limb</td>
<td>75, 150, and 300 units of BoNT-A</td>
<td>Elbow and wrist flexors</td>
<td>(+) Global assessment: 75-unit and 300-unit groups</td>
</tr>
<tr>
<td>Kirazli et al. (1998)10</td>
<td>1b-minus</td>
<td>Randomized, double-blind, parallel-group (BoNT-A vs. phenol)</td>
<td>Lower limb</td>
<td>400 units of BoNT-A or 3 ml of 5% phenol</td>
<td>Ankle planar flexor and foot inverter</td>
<td>(+) ASH superiority for BoNT-A vs. phenol at weeks 2 and 4</td>
</tr>
<tr>
<td>Richardson et al. (2000)11</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Upper limb, lower limb</td>
<td>30–500 units of BoNT-A</td>
<td>Muscles of the upper and lower limbs</td>
<td>(+) MAS: aggregate scores summed from weeks 3, 6, 9, and 12</td>
</tr>
<tr>
<td>Brashear et al. (2002)12</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Upper limb, stroke</td>
<td>200–240 units of BoNT-A</td>
<td>Wrist, finger, and thumb flexors</td>
<td>(+) DAS at week 6</td>
</tr>
</tbody>
</table>

**Key:** (+) = positive (significant) outcome; (–) = negative (not significant) outcome.

9HPT = Nine-Hole Peg Test; ADE = adverse event; AFD = Assessment of Functional Disability; ASH = Ashworth Scale; BoNT-A = botulinum neurotoxin type A (Botox); BoNT-B = botulinum neurotoxin type B (Myobloc); DAS = Disability Assessment Scale; FIM = Functional Independence Measure; GOS = Glasgow Outcome Scale; JHTF = Jebsen Test of Hand Function; MAS = Modified Ashworth Scale; MGAS = Modified Goal Attainment Scale; RAND-36 = RAND 36-Item Health Survey (Short-Form-36); RMAS = Rivermead Motor Assessment Scale; ROM = range of motion; SF-36 = 36-Item Short-Form Health Survey; SRPS = Subjective Rating of Problem Severity; UPDRS = Unified Parkinson’s Disease Rating Scale.
of Hand Function, for BoNT-B compared with placebo.

In the safety assessment, dry mouth occurred in 89% of the subjects in the BoNT-B group and in 20% of those in the placebo group (Level 1b evidence).

**The Childers Study**

In a double-blind, placebo-controlled, dose-ranging study, Childers et al. (2004) randomly chose 91 patients with post-stroke, upper-limb spasticity to receive up to two treatments with 90, 180, or 360 units of BoNT-A or placebo using EMG guidance. Concentrations were varied to keep the volume constant at 4 ml.

Compared with placebo, significant mean reductions in wrist flexor tone, as measured by the Modified Ashworth Scale, were observed with BoNT-A 360 units at weeks one, two, three, six, and nine ($P \leq .005$); with BoNT-A 180 units at weeks one, three, and six ($P \leq .046$); and with BoNT-A 90 units at weeks one, three, six, and nine ($P \leq .034$).

The results supported a dose-dependent response to BoNT-A, because the 360-unit group showed the largest response, compared with the placebo group, at all follow-up visits. Significant improvements over placebo in elbow flexor Modified Ashworth Scale scores were also observed with BoNT-A 360 units ($P \leq .045$) and with BoNT-A 180 units ($P \leq .029$) at weeks one to five and at week nine.

Improvements in finger flexor Modified Ashworth Scale scores were less robust, but they were significant at weeks one and three for the BoNT-A 360-unit group ($P \leq .003$). Significant, superior responses to treatment on the Global Assessment Scale were observed with 360 units ($P \leq .001$) and 180 units ($P \leq .013$), compared with placebo, but no dose dependence was evident.

Generally, no differences were observed throughout the 24-week trial between the groups in functional disability, subjective pain, function (according to the Functional Independence Measure), or quality of life (according to the 36-Item Short-Form Health Survey).

Mild-to-moderate treatment-related ADEs occurred more frequently among subjects in the BoNT-A group, including severe arm pain and injection-site hematomata formation.

This study represented Level 1b-minus evidence and was downgraded because subject retention was below 80%.

### TABLE 5 Level of Evidence Rating of Spasticity and Botulinum Neurotoxin Studies (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Level of Evidence</th>
<th>Study</th>
<th>Spasticity Diagnosis/ Etiology</th>
<th>Dose</th>
<th>Injection Site</th>
<th>Outcome Measures/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brashear et al. (2004)</td>
<td>1b</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Upper limb</td>
<td>10,000 units of BoNT-B</td>
<td>Elbow, wrist, and finger flexors</td>
<td>ASH at all time points except week 2 (wrist only)</td>
</tr>
<tr>
<td>Childers et al. (2004)</td>
<td>1b-minus</td>
<td>Randomized, double-blind, placebo-controlled, dose-ranging</td>
<td>Upper limb</td>
<td>90, 180, and 360 units of BoNT-A</td>
<td>Elbow, wrist, and finger flexors</td>
<td>MAS, with dose-dependent response generally observed</td>
</tr>
<tr>
<td>Verplancke et al. (2005)</td>
<td>1b-minus</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group</td>
<td>Lower limb</td>
<td>Casting + 400 units of BoNT-A or saline</td>
<td>Gastocnemius and soleus muscles</td>
<td>ROM: casting plus BoNT-A vs. control (+13.59 degrees vs. +4.59 degrees) ($P = .07$)</td>
</tr>
</tbody>
</table>

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**Botulinum for Spasticity in Adults**

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Botulinum for Spasticity in Adults

**FIGURE 1** Algorithm for the management of spasticity with botulinum toxin.

The development of a spasticity management program begins with an evaluation of the upper motor neuron syndrome and the determination that spasticity is interfering with patient function. By carefully defining the goals of treatment, the components of the treatment plan are established.

For some patients (e.g., those with spinal cord injury), an important initial treatment may be the removal of noxious stimuli, such as tight orthotics or ingrown toenails. Range-of-motion exercises are indicated for almost all patients to prevent contracture. Oral medications, phenol neurolysis, surgery, and intrathecal baclofen may be useful in properly chosen patients.

Botulinum toxin (BTX) therapy is often the appropriate treatment for patients with spasticity who have focal, dynamic (not fixed) contracture, if spasticity is interfering with function. Careful definition of the goals of BTX therapy is necessary before treatment proceeds. The clinical team helps patients and caregivers identify and clarify goals, and it evaluates the suitability of BTX to meet these goals. Outcome measures, selected for their relevance to the expected benefits of treatment, are applied before the first injection and then again at an appropriate interval following treatment.

An initial dose may be determined from the accompanying dosing chart, but most clinicians adapt and modify these guidelines based upon the individual patient’s response to therapy. In the treatment of spasticity, BTX injection is almost never used as monotherapy, and adjunctive treatments including physical interventions (range-of-motion exercises, serial casting,
or strengthening programs) are instituted or modified after the injection.

When the goals of BTX treatment have been defined and outcome measures chosen, evaluation of the treatment’s success should be straightforward. When the goals of patients or caregivers have not been met despite functional improvement, the clinical team works with them to re-evaluate their expectations.

When the functional or technical goals of treatment have not been met, some modification of muscle selection, injection technique, or adjunctive therapies might be needed. Continued lack of efficacy even with optimal technique and muscle selection suggests that the patient was poorly selected for BTX therapy, the technical goals were inappropriate, or the patient was resistant to BTX. Antibody or frontalis muscle testing may be indicated in this situation.

Successful treatment does not obviate the need for re-evaluation of goals, the treatment program, or the dose and injection site. These matters are routinely considered at the follow-up visit, and adjustments made as needed or desired.

As always, patients and caregivers remain at the center of the decision-making process. ADL = activities of daily living; CP = cerebral palsy; CVA = cerebrovascular accident; MS = multiple sclerosis; OT = occupational therapy; PT = physical therapy; SCI = spinal cord injury; TBI = traumatic brain injury.

The Verplancke Study\textsuperscript{15}

Using a randomized, double-blind, placebo-controlled, parallel-group design, Verplancke et al. (2005) compared BoNT-A and placebo in combination with serial casting to prevent worsening of lower-limb spasticity in patients with traumatic brain injury. Thirty-five patients were selected to receive physiotherapy without casting, gastrocnemius and soleus injections of saline with casting, or gastrocnemius and soleus injections of BoNT-A with casting (total dose: 200 units, diluted at 50 units/ml).

Improvement in the mean angle of ankle dorsiflexion for the patients receiving BoNT-A plus casting was 13.59 degrees (range, −10 to +20 degrees), compared with 11.69 degrees (range, −22 to +22 degrees) for the saline-plus-casting group and 4.59 degrees (range, −20 to +20 degrees) for the physiotherapy group. There was no significant difference between the casting groups.

Baseline Modified Ashworth Scale scores were significantly reduced for both casting groups at week 12 (at the study exit) (saline, $P < .03$; BoNT-A, $P = .04$). The BoNT-A group with casting experienced greater improvement at week 12 on the Glasgow Outcome Scale (4.1), compared with either the saline-plus-casting group (3) or the physiotherapy group (2.8), with scores of 1–3 indicating severe disability; however, the differences were not significant.

No patients in the BoNT-A group with casting required rescue treatment because of their greatly reduced range of motion; however, about 30% of patients in the other treatment groups did need it.

The BoNT-A patients with casting reported only one treatment-related ADE—transient flu-like symptoms. The study represented Level 1b-minus evidence and was downgraded because of incomplete reporting of statistical analyses.

CONCLUSION

The studies reviewed in this article—except Brashear’s trial in 2004,\textsuperscript{13} which used BoNT-B (Myobloc)—reported significant reductions in BoNT-dependent muscle tone. Tone reduction, although not a therapeutic goal, is an important part of a comprehensive spasticity-management program aimed at achieving functional outcomes such as improved gait, hygiene, and pain reduction. Ideally, this systematic review would culminate with a meta-analysis of the studies identified by the search methodology. However, statistical pooling of the results from these studies requires a high level of homogeneity of effect measures for all of the studies.\textsuperscript{16} Even though the identified trials, individually, were of relatively high quality (six Level 1b studies and three studies slightly downgraded to Level 1b-minus, according to the OCEBM criteria), the large degree of heterogeneity between the studies precluded pooling of the study data to improve the power of the analysis.

Function-based outcome measures yielded mixed results. The 2002 Brashear study\textsuperscript{12} showed significant improvement in patient- and caregiver-selected functional goals (on the Disability Assessment Scale) following BoNT-A treatment.

Kirazli et al. (1998)\textsuperscript{10} observed significant improvement in ambulation (walking velocity) in patients receiving BoNT-A, but other investigators did not discern any significant treatment benefit from BoNT-A in standard functional assessments.\textsuperscript{9,11,14} Subjective global assessments of treatment outcomes by patients and physicians tended to be significantly better for BoNT-A patients than controls,\textsuperscript{9,12,14} but differences between groups in standard quality-of-life measures were not observed.\textsuperscript{9,14}

Perhaps these findings underscore the fact that monotherapy with BoNT-A (or any relevant treatment option) is insufficient for managing spasticity in some patients and that it should therefore be incorporated into an overall treatment program that includes physical and occupational therapies, oral medications, intrathecal baclofen, phenol injections, and surgery. We endorse the treatment algorithm put forth by the Spasticity Study Group in 1997 and updated in 2002 (see Figure 1, page 672).\textsuperscript{3,17} We note that no current evidence exists to support the use of BoNT to prevent the onset of spasticity.

A wide variety of BoNT-A concentrations (18–100 units/ml) were used in these studies. EMG was used primarily to identify muscles, but electrical stimulation and surface landmarks were also used. Because of this heterogeneity, we could not definitively determine an optimal concentration of BoNT-A or a preferred method of muscle localization to treat spasticity.

BoNT-A was well tolerated; most treatment-related ADEs were mild to moderate and then resolved. Transient injection-site pain was the most commonly reported ADE. No serious treatment-related events were reported except for individual incidents of arm pain and hematoma, neither of which prompted discontinuation from the study.\textsuperscript{14} There were no significant between-group (BoNT vs. control) differences in the incidence of ADEs, although dry mouth occurred in 89% of subjects in the BoNT-B group, in contrast to 20% of patients in the placebo group.\textsuperscript{13}

Of the nine studies, six were classified as Level 1b, and three studies were Level 1b-minus, according to the OCEBM level of evidence criteria with the evidence supporting a recommendation grade of A (see Tables 3 to 5).

Our Neurotoxin Spasticity Consensus Group acknowledges that several clinical trials using BoNT-A (Dysport) to treat adult focal spasticity have been published. Although this treatment is currently not available in the U.S., we recognize that these studies generally support our conclusions for BoNT-A (Botox).

The Consensus

- Level 1b evidence supports the efficacy and safety of BoNT-A (Botox) for the treatment of focal spasticity in adults, as measured by the Ashworth or Modified Ashworth Scales.
- Based on the reviewed evidence, patients in whom improvement in passive range of motion would be expected to provide functional benefit and/or facilitate care, would be considered the best candidates for BoNT-A treatment.
- The majority of the evidence reviewed addresses spasticity secondary to stroke. Patients with spasticity from other causes (traumatic brain injury, MS, and spinal cord injury) were included in some studies, and they experienced similar treatment outcomes. Despite a lack of randomized, controlled trials focused on patients with spasticity from non-stroke causes, it is reasonable to expect that they would similarly benefit from BoNT-A treatment.
- Because only one small study evaluated the use of BoNT-B (Myobloc/Neurobloc) in the treatment of adult focal spasticity, no definite conclusions about its use in this indication can be made.

continued on page 682
No serious treatment-related ADEs were seen with the use of BoNT-A.

Based on the conclusions of this review, we endorse the treatment algorithm put forth by the Spasticity Study Group in 1997 and updated in 2002.

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REFERENCES