Practice Parameter: Pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society

ABSTRACT

Objective: To evaluate published evidence of efficacy and safety of pharmacologic treatments for childhood spasticity due to cerebral palsy.

Methods: A multidisciplinary panel systematically reviewed relevant literature from 1966 to July 2008.

Results: For localized/segmental spasticity, botulinum toxin type A is established as an effective treatment to reduce spasticity in the upper and lower extremities. There is conflicting evidence regarding functional improvement. Botulinum toxin type A was found to be generally safe in children with cerebral palsy; however, the Food and Drug Administration is presently investigating isolated cases of generalized weakness resulting in poor outcomes. No studies that met criteria are available on the use of phenol, alcohol, or botulinum toxin type B injections. For generalized spasticity, diazepam is probably effective in reducing spasticity, but there are insufficient data on its effect on motor function and its side-effect profile. Tizanidine is possibly effective, but there are insufficient data on its effect on function and its side-effect profile. There were insufficient data on the use of dantrolene, oral baclofen, and intrathecal baclofen, and toxicity was frequently reported.

Recommendations: For localized/segmental spasticity that warrants treatment, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A). There are insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin type B (Level U). For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment (Level B), and tizanidine may be considered (Level C). There are insufficient data to support or refute the use of dantrolene, oral baclofen, or continuous intrathecal baclofen (Level U).

Neurology® 2010;74:336–343

GLOSSARY

AAN = American Academy of Neurology; AE = adverse event; AS = Ashworth scale; BoNT-A = botulinum toxin type A; BoNT-B = botulinum toxin type B; CP = cerebral palsy; FDA = Food and Drug Administration; GAS = Goal Attainment Scale; GMFM = Gross Motor Function Measure; ITB = intrathecal baclofen; MAS = Modified Ashworth scale; OT = occupational therapy; PT = physiotherapy; QUEST = Quality of Upper Extremity Skills Test; TS = Tardieu scale.

The prevalence of cerebral palsy (CP) was recently reported to be 3.6 cases per 1,000 in 8-year-old children,1 with very little variation among Western nations.2 More than 10,000 babies born in the United States each year will be affected by CP.3 CP is the most common cause of spasticity in children, and the majority of children with CP are affected by spasticity.4 The Taskforce on Childhood Motor Disorders defines spasticity as “hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement; 2) resistance to externally imposed movement rises rapidly above a threshold speed of joint angle.”5
Spasticity is one component of the multifaceted motor disability of CP and may not be the main factor interfering with function, participation, or activity. Alleviation of spasticity may not always be desirable; some patients may experience a decline in function with spasticity reduction. The decision to use antispasticity medications requires careful assessment of the patient’s other impairments (e.g., weakness, movement disorders) and proper selection and use of the treatment. Reasons to treat spasticity include reducing pain and muscle spasms, facilitating brace use, improving posture, minimizing contractures and deformity, facilitating mobility and dexterity, and improving patient ease of care as well as hygiene/self-care.

Several tools such as the Ashworth scale (AS) and the Modified Ashworth scale (MAS) have been used in clinical trials, with the assumption that they measure spasticity. These scales measure a broader set of neural and musculoskeletal factors of non-velocity-dependent hypertonia in addition to spasticity itself. A tool that is more consistent with the proposed definition of spasticity above is the Tardieu scale (TS). The TS accounts for the joint angle measure of the spastic phenomenon at different velocities of joint movement.

Over the last 20 years, several pharmacologic antispasticity treatments have been adapted for use in patients with CP. These include oral medications like benzodiazepines, dantrolene, baclofen, and tizanidine; neuromuscular blocking agents such as botulinum toxins A and B (BoNT-A and BoNT-B); chemical denervation using phenol and alcohol; and intrathecal baclofen (ITB). Oral medications and ITB are used when a generalized antispasticity effect is desired. Chemical denervation agents are used to treat localized (one extremity) or segmental (lower body, hemibody) spasticity. The mechanisms of action and pharmacology of these drugs are described in other publications.

This article reviews and evaluates published evidence of the efficacy and safety of these medications in children and adolescents affected by spasticity due to CP.

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology (AAN) convened a multidisciplinary author panel consisting of 5 pediatric neurologists, 2 developmental pediatricians, 1 pediatric physiatrist, 1 pediatric orthopedist, and 1 adult neurologist. Literature searches of MEDLINE and EMBASE were conducted for relevant articles published from 1966 to July 2008 using the following key text and index words: cerebral palsy, static encephalopathy, spasticity, hypertonia, children, and infantile. Key text and index words for the intervention included diazepam, Valium, tizanidine, Zanaflex, dantrolene, Dantrium, baclofen, Lioresal, intrathecal baclofen, phenol, alcohol, botulinum toxin A, Botox, Dysport, BTX-A, BoNT-A, botulinum toxin B, BoNT-B, BTX-B, Myobloc, and Neurobloc.

The inclusion criteria were all foreign languages with English abstracts, human subjects, peer reviewed, patients 19 years of age or younger with CP, and more than 9 patients studied. Citations of review articles from 2000 to 2008 were checked for additional pertinent references.

A total of 978 abstracts were initially found. From these, 528 were identified as potentially pertinent and reviewed in full. Finally, 218 articles were selected that fulfilled the inclusion/exclusion criteria.

Each article was reviewed, abstracted, and classified by at least 2 authors. Disagreements were resolved by reaching consensus among the reviewers, the first author, and at least 2 other authors. The AAN’s 4-tiered classification scheme for therapeutic evidence was used to classify articles (appendix e-3 on the Neurology Web site at www.neurology.org), and the strength of the recommendation was linked to the evidence (appendix e-4).

ANALYSIS OF EVIDENCE

Treatment of localized or segmental spasticity. There were no publications on phenol, alcohol, or BoNT-B that met criteria for review.

A total of 148 studies using BoNT-A to reduce spasticity in children with CP met eligibility criteria. Fifteen studies were Class I and 5 were Class II (table e-1). Five of these studies assessed the effect of BoNT-A in the upper extremity; the rest assessed only the lower extremity. A total of 573 children received BoNT-A in the Class I and II studies. The majority of the studies included children as young as 2 years of age. Spasticity was measured using the AS or the MAS in 13 of the 20 studies. The BoNT-A doses used are indicated in table e-1.

Spasticity reduction. Spasticity reduction was reported in all but 3 studies. In one study, spasticity was significantly reduced by electromechanical measure but not by AS. Spasticity was reduced at 2 weeks (p = 0.0001), 4 weeks (p < 0.001), and 3 months (p = 0.01) after treatment.

One Class I study provided information regarding the degree of spasticity improvement. This study compared the effect of BoNT-A lower extremity treatment combined with physiotherapy (PT) vs PT alone and reported a mean increase in score on the MAS (increased tone) after 6 months (approximately half of an MAS point) in the control group, whereas the BoNT-A group showed a mean decrease in MAS.
score (decreased tone) 6 months after injection (approximately 1 MAS point) ($p < 0.05$).26

**Lower extremity functional improvement.** A Class I dose-comparison parallel study found a significant dose-effect correlation in gait kinetics and kinematics using 3-dimensional gait analysis.27 The high-dose group showed greater ankle dorsiflexion in stance ($p < 0.001$) and swing ($p < 0.05$) at 4 weeks than at baseline; these differences were not seen in the low-dose group. The high-dose group also showed a longer effect than the low-dose group, demonstrating increased ankle dorsiflexion during stance at 12 weeks compared to baseline ($p < 0.01$). A Class I study ($n = 40$; spastic diparesis and hemiparesis) reported significant functional lower extremity improvement by the Gross Motor Function Measure (GMFM) walking dimension 12 weeks after BoNT-A treatment in the lower extremities. Of patients treated with BoNT-A, 37% (7/19) (mean improvement 9.7%) showed improvement compared with 7% (1/15) in the placebo group ($p = 0.04$). A Class II study that measured functional improvement by the Goal Attainment Scale (GAS) reported that 11 of 33 (33%) functional ability goals were achieved by 7 of 11 children with CP after BoNT-A treatment in the lower extremities ($p = 0.001$).29 Gait improvement was reported by using the Physician Rating Scale in a Class I study.26 The mean improvement change was twice as great in the treated group as in the placebo group 12 weeks after treatment ($p = 0.02$).

In contrast, 3 Class I placebo-controlled studies—($n = 64$),21 ($n = 125$),30 and ($n = 52$)31—using the same BoNT-A preparation at slightly higher dose (30 U/kg vs 25 U/kg) and the same outcome measure (GMFM) failed to demonstrate a significant functional improvement, despite significant improvements in ankle dorsiflexion30 4 weeks after injections and initial foot contact31 16 weeks after injections.

**Upper extremity functional improvement.** The effect of BoNT-A treatment on upper extremity function in children with hemiplegic CP was measured using the Quality of Upper Extremity Skills Test (QUEST) in 4 Class I studies.17-20 One study ($n = 42$),18 which compared the effect of a single low-dose, high-concentration BoNT-A treatment plus occupational therapy (OT) to OT alone, found upper extremity functional improvement at 1 month ($p < 0.001$) and 3 months ($p < 0.001$) but not at 6 months after treatment. A larger proportion of treatment group subjects showed more than 20% change above baseline QUEST scores compared with the control group at 1 month (67% vs 19%; $p = 0.004$) and 3 months (71% vs 33%; $p = 0.03$) but not at 6 months. Application of BoNT-A in this study was guided by electrical stimulation. In another Class I study ($n = 29$),17 BoNT-A was injected into upper extremity muscles using anatomic knowledge only to guide injection location. The study used the same BoNT-A formulation and similar doses, demonstrating an improvement in QUEST scores at 1 month ($p < 0.05$) but not at 3 or 6 months after treatment. In a small Class II study ($n = 14$)16 in which BoNT-A was injected using anatomic knowledge only to guide injection location, despite an increase in maximum active elbow and thumb extension ($p = 0.02$ and $p = 0.03$) and a reduction of tone in the wrist and elbow ($p = 0.003$ and $p = 0.01$) 2 weeks after BoNT-A treatment, only a modest improvement in hand function was reported by the grasp-and-release score measure at 12 weeks ($p = 0.01$). However, no improvement was noted in fine motor function, assessed by the ability to pick up coins, and in some cases this ability deteriorated temporarily. A Class I study ($n = 80$) demonstrated a much higher functional benefit when BoNT-A was used in combination with OT than when used alone.19

**Adverse events.** Specific adverse events (AEs) were reported in 17 studies (table e-1). All were transient and did not require hospitalization. The most common AEs were localized pain, excessive weakness, unsteadiness and increased falls, and fatigue. Urinary incontinence was reported in 5 patients and dysphagia in 2 patients. No deaths were reported.

**Conclusions.** For children with CP, BoNT-A is established as an effective treatment to reduce spasticity in the upper and lower extremities (Class I and II evidence), but there is conflicting evidence regarding functional improvement. The available evidence suggests that BoNT-A is generally safe in children with CP. However, severe generalized weakness may occur.

**Recommendations.**

1. For localized/segmental spasticity in the upper and lower extremities of children with CP that warrants treatment, BoNT-A should be offered as an effective and generally safe treatment (Level A). There is insufficient evidence to support or refute the use of BoNT-A to improve motor function in this population (Level U).

2. There is insufficient evidence to support or refute the use of BoNT-B, phenol, and alcohol injections as a treatment for spasticity in children with spastic CP (Level U).

**Clinical context.** At the time of this writing, the Food and Drug Administration (FDA) has not approved BoNT-A for the treatment of spasticity in children. BoNT-A is approved for the treatment of spasticity in children and adults in Canada and several other countries. Different formulations are not bioequiva-
lent and may have different therapeutic efficacy and safety profiles.\textsuperscript{32,33}

The AAN recently published an evidence-based review on the safety and efficacy of BoNT for the treatment of adult and childhood spasticity.\textsuperscript{34} A Level A recommendation was given for the use of BoNT-A as a treatment of spasticity in the lower extremities (equinus and hip adductor spasticity) and a Level B recommendation was given for the treatment of spasticity in the upper extremities of children with CP.

It is common practice to use BoNT-A in combination with serial casting, orthoses, and PT and OT.\textsuperscript{19} Typically, there is a 3- to 4-month clinical response requiring repeated injections. Some experts recommend using the smallest dose of BoNT-A and avoiding injecting more frequently than every 3 months to minimize the risk of antibody resistance.\textsuperscript{35}

On the basis of postmarketing reports from its Adverse Event Reporting System, the FDA released on February 8, 2008, an “early communication” describing a “relative handful of systemic reactions” after BoNT injection (A or B) for limb spasticity associated with CP. At the time of this writing, the FDA has not completed the review of reported serious AEs related to BoNT, and has made the following recommendations: 1) understand that potency determinations expressed in “Units” or “U” differ among the BoNT products; clinical doses expressed in units are not comparable from one botulinum product to the next; 2) be alert to the potential for systemic effects following administration of BoNT such as dysphagia, dysphonia, weakness, dyspnea, or respiratory distress; 3) understand that these effects have been reported as early as 1 day and as late as several weeks after treatment; 4) provide patients and caregivers with the information they need to be able to identify the signs and symptoms of systemic effects after receiving an injection of BoNT; 5) tell patients they should receive immediate medical attention if they have worsening or unexpected difficulty swallowing or talking, trouble breathing, or muscle weakness.

**Treatment of generalized spasticity.** Seventy studies using oral antispasticity medications and ITB were identified, and 20 met selection criteria: 4 used diazepam,\textsuperscript{36–39} 5 used dantrolene,\textsuperscript{40–42} 1 used both,\textsuperscript{43} 3 used oral baclofen,\textsuperscript{7,46,47} 1 used tizanidine,\textsuperscript{48} and 6 used ITB.\textsuperscript{49–54}

**Diazepam.** Regarding diazepam treatment, we identified 1 Class I study,\textsuperscript{36} 2 Class II studies,\textsuperscript{41,42} and 2 Class IV\textsuperscript{53,54} studies met the selection criteria (table e-2). The Class I study and 1 of the Class II\textsuperscript{41} studies found conflicting results using a similar dose of 4–12 mg/kg/day. The Class I study found no spasticity improvement, no functional gain, and strength reduction (\(p = 0.013\)). The Class II study,\textsuperscript{41} which used a within-subject crossover design, found spasticity improvement (not graded) with changes in the neurologic examination (tone, tendon reflexes, clonus) (\(p < 0.01\)). Although there was no change in gross motor function, activities of daily living (including coordination in dressing and eating, control of limbs in spontaneous play, stamina, freedom of movement, and facilitation of therapy) improved during the treatment period compared to baseline (\(p < 0.02\)). Improvement in reflexes (\(p < 0.005\)) and reduced scissoring (\(p < 0.05\)) were reported in the other Class II study.\textsuperscript{52} AEs were found in 30% to
60% of the patients and included fatigue, irritability, drowsiness, anorexia, and gastrointestinal symptoms (e.g., vomiting and diarrhea). Four of 9 children who continued taking dantrolene after the study was completed developed or had exacerbations of seizures.6

Conclusions. There is conflicting evidence regarding the effectiveness of dantrolene in reducing spasticity in children with CP. Dantrolene frequently causes side effects such as weakness, drowsiness, and irritability in children with spastic CP.

Recommendation. There is insufficient evidence to support or refute the use of dantrolene for the treatment of spasticity in children with CP (Level U).

Clinical context. On the basis of the author panel’s experience, dantrolene is rarely used in clinical practice to reduce spasticity in children with CP. This may be due to the lack of evidence in the literature to support its efficacy and the general concern regarding its potential frequent and/or serious AEs. Although dantrolene has been associated with hepatotoxicity,6,15 none of the studies reviewed reported this AE in children, perhaps due to the small number of subjects included in these investigations.

Baclofen (oral). Two Class II studies7,67 and 1 Class IV study8 met selection criteria (table e-2). The Class II studies showed conflicting results. A double-blind crossover trial in 20 children 2–16 years old receiving a dose of 10–60 mg/day found a reduction in spasticity by means of the AS (p < 0.001).7 After 28 days of treatment, 14 patients improved at least 1 level and 5 improved more than 1 level. Only 2 patients improved while taking placebo. Spasticity improvement was demonstrated by increased passive range of motion, seen in 11 patients (p < 0.001). Ten patients who were able to walk without assistance prior to treatment showed no significant functional improvement. Furthermore, one patient who relied on the spastic “crutch” to ambulate showed walking impairment after treatment as the underlying weakness was manifested. The other Class II study,67 a double-blind placebo crossover trial (n = 15) using a similar dose and age group, was powered to detect a difference as measured by the GAS but not for other measures. Although improvement on the GAS was reported (p = 0.05), there was no improvement in spasticity (modified TS) or functional benefit measured using the Pediatric Evaluation of Disability Inventory at 12 weeks. The first study found AEs in 25% of patients taking the medication, and no AEs were noticed in those taking placebo. Side effects included somnolence or sedation (20%) and hypotonia (15%) that resolved after drug discontinuation. The second study did not find a significant difference in AEs between groups.

Conclusions. There is conflicting Class II evidence regarding the effectiveness of oral baclofen in reducing spasticity and improving function in children with CP. Systemic toxicity was found in some patients.

Recommendation. There is insufficient evidence to support or refute the use of oral baclofen for the treatment of spasticity or to improve motor function in children with CP (Level U).

Clinical context. Baclofen is widely used in clinical practice to treat spasticity in children with CP. Experts recommend starting baclofen at the lowest possible dose (5–10 mg/day divided into 3 doses a day)7 to minimize AEs like drowsiness and sedation. The dose is gradually tapered until discontinuing because abrupt discontinuation may cause withdrawal symptoms, including increased spasticity, hallucinations, confusion, hyperthermia, and seizures.13

Tizanidine. One small Class II8 placebo-controlled parallel study treated 10 children with a mean age of 4.1 years (range 2–15) with tizanidine 0.05 mg/kg/day and 30 children with placebo for 6 months (table e-2). A reduction in spasticity (p = 0.0001) was found beginning 2 weeks after initiating treatment and was sustained throughout the trial. Postural and reflex improvement was also reported (p = 0.0001). No functional assessments were done. No side effects were found, and liver enzymes remained normal throughout the duration of the study.

Conclusions. Tizanidine is possibly effective to treat spasticity in children with CP. No toxicity was found in this small study.

Recommendation. Tizanidine may be considered for the treatment of spasticity in children with CP (Level C). There is insufficient evidence to support or refute the use of tizanidine to improve motor function in this population (Level U).

Clinical context. Tizanidine’s antispasticity effect has been demonstrated in adults with multiple sclerosis and spinal cord injury.7,16 Little information is available to assist practitioners with the effective use of this drug to treat spasticity in children. Because tizanidine is extensively metabolized by the liver, hepatic impairment may have a significant effect on its pharmacokinetics. AEs related to tizanidine use in adults include hypotension, sedation, asthenia, dry mouth, dizziness, hallucinations, and hepatotoxicity. Their incidence in pediatric patients has not been studied.

Intrathecal baclofen pump. One Class III study9 and 5 Class IV studies10–14 assessing ITB met inclusion criteria (table e-3). All studies reported reduced spasticity in children with CP.

Occasional headache, vomiting, lethargy, disorientation, agitation, irritability, and meningitis were reported in 2 of the Class IV studies.10,14 CSF leaks (17%), seromas (29%), catheter malfunction (43%),
and wound infection (39%) were reported more frequently.

**Conclusion.** Data are inadequate concerning the use of continuous ITB as an antispasticity treatment in children with CP. CSF leaks, seromas, catheter-related complications, and wound infection occur frequently, and other, milder complications occur less frequently.

**Recommendation.** There is insufficient evidence to support or refute the use of continuous ITB for the treatment of spasticity in children with CP (Level U).

**Clinical context.** In 1996, ITB received FDA approval to treat spasticity of cerebral origin. A major factor in the lack of Class I and II evidence may be the difficulty of performing a randomized control trial or crossover trial in subjects with ITB pumps. Catheter-related complications, pump pocket collections, and wound infections remain a concern, and ongoing efforts aim to reduce their incidence. One retrospective study of the safety of ITB in children (n = 200) found that 11% had CSF leakage, 7% had catheter-related problems, and 5.5% developed infections.  

**RECOMMENDATIONS FOR FUTURE RESEARCH**

1. The AS has been used by most spasticity studies. It measures muscle resistance to passive movement but fails to describe the velocity of the stretching movement and therefore is inadequate to measure spasticity and distinguish it from other types of hypertonia (e.g., dystonia). Standardized and validated spasticity scales and clinically relevant measures sensitive enough to detect change should be used to qualify and quantify spasticity according to its current definition (e.g., Tardieu Spasticity Scale).

2. None of the oral medications used to treat spasticity in children has been adequately tested for safety and efficacy. There are minimal or no data regarding the pharmacokinetics or appropriate dosing parameters to treat children. These critical questions deserve serious research efforts.

3. The effects of both spasticity and the treatment of spasticity on activity and participation as defined by the International Classification of Function, Disability and Health of the World Health Organization need to be studied in children with CP.  

4. Although there is sufficient evidence to recommend BoNT-A as an effective antispasticity treatment in children with CP, its beneficial effects on function, ease of caregiving, activity, and participation need to be established. More data about safety and long-term effects are also needed.

5. The efficacy and safety of BoNT-B, phenol, and alcohol chemodenervation as treatments for spasticity in children with CP need to be determined.

6. The efficacy and safety of oral baclofen and the long-term continuous intrathecal pump administration of this medication need to be determined in children with CP.

7. The few available treatments to reduce generalized spasticity are associated with a high incidence of AEs and complications. There is an urgent need for studies to establish the efficacy of the current therapies and find additional safe and effective treatments to help children affected by generalized spasticity due to CP. A first step could be to investigate medications that have shown antispasticity effect in adult patients (e.g., gabapentin).

**DISCLOSURE**

Dr. Delgado serves on the editorial board of Developmental Medicine and Child Neurology; has received research support from Abbott, Sciele Pharma, Inc., UCB, Allergan, Inc., the Hurst Foundation, the United Cerebral Palsy Research & Educational Foundation, the Linda and Don Carter Foundation, and the Crowley Carter Foundation; and estimates that 50% of his clinical effort is spent on assessment and management of motor disorders of childhood, which includes treating children with cerebral palsy with oral antispasticity medications, ITB, and botulinum toxin injections. Dr. Hirtz reports no disclosures. Dr. Aisen serves as Medical Director of Cerebral Palsy International Research Foundation. Dr. Ashwal serves on the editorial board of Pediatric Neurology; receives royalties from publishing Pediatric Neurology: Principles and Practice (Elsevier, 2006); and receives research support from the NIH [R01 NS054001-01 (PI); R01NS059770-01A2 (PI)]. Dr. Fehlings has received speaker honoraria and funding for travel from RX Media; receives research support from Allergan, Inc., the Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Services (SSHRS), the Bloomview Research Institute, and Physician Services Inc.; and estimates 50% of her clinical effort is spent on spasticity intervention including botulinum toxin injections and ITB. Dr. McLaughlin has received research support from Medtronic, Inc., the NIH [NINDS NO1-HD-3–3351 (site PI), 1 U01 AR52171-01 (site PI), 1RC1 HD063838-01 (site PI)], and United Cerebral Palsy Research & Education Foundation; and spends 10% of his time evaluating and managing children with oral medications, baclofen pumps, and botulinum toxin. Dr. Morrison serves on the editorial boards of the Journal of Child Neurology and Pediatric Neurology; and estimates that <1% of her clinical effort is spent on skin biopsy and <1% on lumbar puncture. Dr. Shrader has received funding for travel from Stryker; and has received research support from Stryker, Smith and Nephew, Biomet, and VQ Orthocare. Dr. Tilton has served on a speakers’ bureau for and received speaker honoraria and funding for travel from Medtronic, Inc.; has received research support from Allergan, Inc.; holds patent rights on a non-neurologic application of botulinum toxin (under consideration for licensure to her institution); and estimates 8%–10% of her clinical effort is spent on botulinum toxin injections and 10%–15% on intrathecal baclofen pumps. Dr. Vargus-Adams receives research support from the NIH [IK23 HD049552 (PI), NICHD-2005-13-2 (Co-I), U01 AR057940-01 (Co-I)] and the Ohio Division of Emergency Medical Systems; her immediate family member holds financial interest in Novartis, Dermik Laboratories, Inc., and Proctor & Gamble and holds equity interest in Proctor & Gamble, Ligand, and GlucoWatch; and estimates 3% of her clinical effort is spent on intrathecal baclofen test dose and management, 15% on botulinum toxin injections, and 2% on phenol nerve blocks.
REFERENCES


Neurology 2010;74;336-343
DOI 10.1212/WNL.0b013e3181cbcd2f

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