Harper Hospital
Detroit Medical Center / Wayne State University

Rehabilitation Institute of Michigan

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RIM SERVICES PEARLS

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B. Anticoagulation

1. Daily determine patients to be followed from antibiotic/anticoagulation download; if not available, it can be printed:

   7.6.3
   Page down to DLY_ABX_HEP.RIM
   Press enter
   Press escape to return to main menu after printing

2. Lab results are found in Sunquest under RB. Hemodialysis patients also have lab results under HH. CIS does not list RIM lab results, though other test results and reports may be available there if done at another DMC site.

   Even though INR/PT was not ordered by pharmacy, one may have been ordered by the physician or just entered on the wrong date; the lab calls outliers to the floor or, if indicated, to pharmacy beeper #9578.

3. Lab results usually are back by 9:30am; check every anticoagulation patient consulted for new labs.

4. Standardized lab draw times are AM (approximately 6-7am), 4pm, and 8pm. Levels ordered at other times are drawn by the RN or PCA but may need to be deferred to the next lab draw if unable to obtain.

   If the morning INR is not done, try to order for the next day instead of ordering later in the day.

5. Order labs at least once daily if on heparin.

   For aPTT orders, write in the chart: ”Comments: Send to stat lab, call #9578 with rush results.”

6. For stable patients on warfarin, order labs Monday, Wednesday, and Friday.

7. An INR or aPTT ordered multiple times (i.e., qd X3) may or may not be entered as intended. Order labs by date(s) needed or daily only.

8. Do order an INR either the day before discharge (preferably) or the day of discharge.

   Discharge dates (when known) are posted on the whiteboard where patients are listed by room number or can be found in the interdisciplinary team report located at the front of the progress note section of the chart.

9. Order CBC a minimum of 1X each week while on warfarin. Patients on heparin need a CBC ordered QOD. Remember, a 2 gram Hgb drop or bleeding must be addressed with the physician.

10. Try to not order INR/PTs on the weekend as there are fewer people to cover.

11. Dr Nasser sends his TKA and THA patients from MISOH to RIM on warfarin and requests a goal INR of 1.6-2 for DVT prophylaxis lasting 3 weeks. He requests that his patients not be started on Lovenox.

12. To track down missing anticoagulation labs or to add an INR/PT or aPTT to blood already drawn, call DRH core lab at 30714. If needed to track a result, HUH processing is 58831.

13. Note that run times are less often than at Harper and Hutzel (6:30am, 10am, 1pm, 4pm, 7pm, and 10pm). When possible, try and order warfarin doses as daily rather than X1 tonight.

    Note that orders written, for example, 5mg po qd X 2 days are often interpreted as on-going by the order entry pharmacist and not reentered if the same dose is continued beyond those 2 days; the patient often receives no further doses. Either write doses as "daily" or "X1 tonight at 1800" to avoid this situation.

14. All patients on warfarin must be counseled and a note left in the chart. This is a Tier 2 policy.

    A note using the preprinted sticker is left in the progress note section of the chart. Coumadin counseling can be done at any point during the patient's stay. Do indicate counseling completed in the appropriate section of the anticoagulation PMR as well.

B. Antibiotics

1. Daily determine patients to be followed from antibiotic/anticoagulation download; if not available, it can be printed:

   7.6.3
   Page down to DLY_ABX_HEP.RIM
   Press enter
   Press escape to return to main menu after printing

2. Note that patients transferring into RIM who are on antibiotics are often on established doses of those antibiotics long term. Profiles may be available from another HUH/HWH/KCC unit.

3. Before changing an admission dose, try to locate the transfer chart and verify if any levels have been done and any adjustments made at the prior facility as well as what day of antibiotic therapy the patient is on.

4. If transferred from a DMC facility, often levels can be found on line and the old chart can indicate the timing of the transfer antibiotics. The nursing transfer report should indicate when the last dose of antibiotic was administered.

5. Levels are often indicated in the first week at RIM because the patients no longer have a running IV and fluid status may change enough to warrant changes in dose or frequency.

C. TLOA

1. Patients go home on weekends to assess living arrangements and care needed after discharge; taking their own medications is an important part of that trial.

2. Physicians will indicate which medications and doses to send the patients home on in the standard inpatient order form. Orders for PRN medications need to indicate a quantity. Labels are generated from MS meds.

3. Fill all the TLOA medications indicated including any bulk items and controlled drug items from central pharmacy and place the order with the outpatient prescriptions in the appropriate outpatient prescription file.

4. CII prescriptions need to be written on a regular prescription blank and signed by the physician.

5. Physician DEA numbers can be found on the beeper list kept with the RIM PMRs in Drug Information.

D. Vaccines

1. Pneumococcal and influenza vaccines are kept as floor stock at RIM.

2. Extra vials are kept in the technician's office, room 518, at RIM.

3. Two labels are sent with each dose of vaccine. One label is attached to the MAR when the vaccine is administered, and the other is attached to the continuing patient care (CPC) form given to the patient at discharge.

4. Patient handouts can be found on the pharmweb under antimicrobials.

E. Other medications

1. Baclofen
    a. Note that doses can safely go as high as 240mg daily.

2. Botox
    a. Note that Botox is used on inpatient TBI patients to control spasticity or release contractures and help patients benefit more from inpatient therapies. It is found in the storeroom in the locked refrigerator.
    b. The dose can range from 100-700 units depending on how many sites are to be injected.
    c. The entire vial is dispensed along with a 10ml vial of NS preservative free to be used for reconstitution.

3. Theophylline Study
    a. Note that Dr Nieshoff periodically has study patients on theophylline obtained through our investigational drug department.
    b. The monitoring parameters are attached and the pharmacist is usually consulted to monitor the theophylline levels and doses.

THEOPHYLLINE DOSING (Study I-652)

1. Theophylline level prior to start of therapy
2. Use actual body weight to dose unless patient is obese
3. Use ideal body weight to dose if obese (≥2X IBW)
4. Give doses ATC, i.e., 0800 and 2000 for less variation in peak and trough
5. Start loading dose and first maintenance dose at 0800 or 2000
6. Available doses: Theophylline syrup 80mg/15ml and extended-release tablets 100mg, 200mg, 300mg
7. Loading dose: Check level 1-2 hours after dose given

Criteria	Oral Loading Dose
If no theophylline given previously	5mg/kg oral liquid (Max 400mg)

8. Maintenance dose to start after loading dose; divide into 2 doses/day to be given at 08 and 20

Criteria	Oral Maintenance Dose
Non-smoking adolescents 12-16 years old	13mg/kg/day (1100mg/day)
Non smoking otherwise healthy adults including elderly	10mg/kg/day (Max 900mg/day)
Cardiac decompensation Cor pulmonale Liver dysfunction	5mg/kg/day (Max 400mg/day)
Smoking adolescents or otherwise healthy adults	16mg/kg/day (1400mg/day)

9. Potential interactions

Decrease Clearance And potentially increase theo levels	**Increase Clearance** And potentially decrease theo levels
Allopurinol Cimetidine Ciprofloxacin Clarithromycin Erythromycin Propranolol Thiabenazole Ticlopidine Zileutin Systemic viral illness	Carbamazepine Phenytoin Phenobarbital Rifampin Sulfinpyrazone Smoker Charcoal broiled meat High protein diet

10. Adverse Drug Reactions
    a. GI upset
    b. Headache
    c. CNS stimulation
    d. Diuresis
    e. Arrhythmias
    f. Seizures

11. Check levels/dosage adjustment
    a. Monitor peak levels at least 48hrs after no missed doses
    b. Check levels 2X week after AM dose and 48-72 hours after any dosage change
    c. Note: For every 1mg/kg theophylline given, blood levels will increase 2mcg/ml
    d. Blood sample 1-2 hours after loading dose (immediate release liquid)

e. Blood sample 4-6 hours after morning dose of Slo-bid (Evening serum concentrations may be less reliable because of diurnal rates of absorption—slower at night)

Theophylline Range	Theophylline Level	Adjustment	Comments
Normal	10-12 mcg/ml	continue same dose	Continue same dose unless potential DI or side effects present
	12-15 mcg/ml	Occasional intolerance requires a 10% ↓	No dose change needed unless side effects present
Too High	16-20 mcg/ml	↓ by 10-25%	Even if asymptomatic and side effects absent, a dose ↓ is prudent
	20-24.9 mcg/ml	↓ by 50%	Omit one dose even if asymptomatic and side effects absent, a dose ↓ is indicated
	25-29.9 mcg/ml	↓ by > or = 50%	Omit next 2 doses even if asymptomatic and side effects absent; a dose ↓ is indicated; repeat serum theophylline concentration after dose adjustment
	≥30 mcg/ml	Omit next 4 doses; ↓ by 60-75%	Seek medical attention and consult regional poison center even if not symptomatic; if > or = 60 years of age, anticipate need for treatment of seizures
Too Low	<5mcg/ml	↑ dose by 25%	Recheck serum theophylline concentration
	5-9.9 mcg/ml	↑ dose by 10-15%	Recheck serum theophylline concentration

Whenever side effects occur, decrease dose to previously tolerated lower dose

12. Patient information: See study protocol

13. Monitor
    a. Heart rate
    b. CNS effects (insomnia, irritability)
    c. Respiratory rate
    d. Serum theophylline level
        i. 0.5-1ml in red top tube
        ii. therapeutic level 10-15mcg/ml

14. Exclude patients with
    a. See study protocol
    b. Currently on theophylline, aminophylline or pentoxiphylline?

15. Sources
    a. Koda-Kimble, et al., Applied Therapeutics: The Clinical Use of Drugs, 2001
    b. Dipiro, et al., Pharmacotherapy: A Pathophysiologic Approach; 1999
    c. Lacy, et al., Drug Information Handbook, 1999

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ANTISPASTICITY MEDICATIONS

Patricia W. Nance, MD, and Robert R. Young, MD

In patients with neurologic impairment, the management of spasticity is a therapeutic challenge. Although the purpose of this article is to review the pharmacologic treatments of spasticity, it is important to note that spasticity frequently occurs in the presence of other clinical signs and symptoms of the upper motor neuron syndrome. The presence of spasticity is not automatically an indication to initiate pharmacologic treatment because involuntary muscle tone can be beneficial to patients with loss of voluntary muscle power by enabling them to stand with assistance, to transfer in or out of a wheelchair, to dress, and so on. Frequently, however, spasticity can be perceived as bothersome, functionally limiting, painful, or causing loss of sleep.[96] When severe, violent muscle spasms can cause episodes of apnea, long bone fractures, joint dislocations, and chronic skin ulceration.

Spasticity has been defined in many ways by many different authors; Lance, however, defined spasticity as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon reflexes resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome."[47] The upper motor neuron syndrome is a constellation of many symptoms that can be separated into positive and negative types. Spasticity would be an example of a positive symptom; lack of coordination, weakness, or paralysis would all be examples of negative symptoms. It is important to keep the constellation of upper motor neuron symptoms in mind because positive and negative symptoms often coexist, and the treatment of one may affect others. In addition, it should be

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borne in mind that functional limitations often attributed to positive symptoms such as spasticity may in fact be related to the lack of voluntary control or weakness that is a negative symptom.

Spasticity has been identified as a problem by 67% of patients with spinal cord injuries.[58] In 40% to 60% of patients with multiple sclerosis, fatigue, pain, and spasticity are all identified as significant problems.[9, 15] Severe, uncontrolled spasticity can cause reduced joint mobility and contractures, difficulty moving joints and poor hygiene, difficulty with bladder catheterization, and sleep disturbances. The initial approach to the treatment of spasticity is to assess any recent or sudden changes in the level of tone in a search for a spasticity aggravating factor. In general, spasticity aggravating factors are any lesion or abnormality that produces a nociceptive stimulus, such as a bladder infection, bowel distention due to chronic constipation, a long bone fracture or joint dislocation, a deep vein thrombosis, an in-grown toenail, or skin ulceration. Occasionally, alleviation of a treatable aggravating factor reduces or eliminates the need for further symptomatic treatment of the spasticity.

The functional limitations caused by the spasticity should be identified and ranked in terms of relative importance to the patient. An agreed upon level of improvement in the most important function could then be a goal of treatment. A validated and standardized method for this type of assessment is available.[73] Clinical quantification of spasticity severity should be applied for each patient visit. A commonly used clinical scale is the Ashworth scale (Table 1).[3] Patients should be encouraged to maintain an ongoing exercise program, including passive stretching as well as an active exercise regime.[11, 38] To decide upon which specific antispasticity medication to prescribe, one should consider the anticipated therapeutic effects and the potential adverse side effects.

A GENERALIZED APPROACH TO TITRATION

Because spasticity treatment is symptomatic and not curative, modification of the prescription depends upon the patient's specific needs and individual responsiveness to the prescribed medication. For example, if the patient's main problem is frequent awakening due to episodic painful spasms at night, the initial dosing would be at bedtime. If the patient's main problem is excessive stiffness upon awakening in the morning, the initial prescription should provide for an early morning dose. One week following initiation of the prescription, the patient should be re-examined and a titration schedule established. Table 2 lists the four approved antispasticity drugs and prescribing information. If the medication has a short half-life and the patient is experiencing undesirable on-off effects, then one would recommend an increased frequency of dosing. Typically, one titration dose is added every 3 to 4 days until one of the following occurs: the therapeutic goal is achieved, the maximum recommended dose is reached, or adverse events are intolerable. If the therapeutic goal is reached, maintain the prescription dose and frequency and follow the patient for maintenance of therapeutic effects, monitor blood work as indicated, and watch for potential drug interactions. If the maximum recommended dose is reached without attaining the therapeutic goal, reassess the goal to be sure that it is realistic. To improve therapeutic efficacy of an antispasticity medication, one could combine antispasticity medications or cautiously consider prescribing a dose that is higher than recommended. If intolerable side effects occur, a decrease in the dose likely will reduce the severity or eliminate the effect, and then a second antispasticity medication could be considered.

Table 1. THE ASHWORTH SCALE

With patient in a supine position, levels of tone in the subject's muscles are assessed by resistance to passive range of motion.

0 = No increase in tone
1 = Slight increase in tone, giving a "catch"
2 = More marked increase in tone but limb easily moved
3 = Considerable increase in tone—passive movement difficult
4 = Limb rigid in flexion or extension.

APPROVED DRUGS FOR SPASTICITY TREATMENT

Baclofen (Lioresal)

Baclofen (4-amino-3-[4-chlorophenyl] butanoic acid) is structurally similar to γ-aminobutyric acid (GABA). GABA is one of the main inhibitory transmitters in the central nervous system. Because the inhibitory effects of baclofen are not reversed by bicuculline, the receptors for baclofen are designated as $GABA_B$ receptors. When baclofen activates these receptors the neuron becomes hyperpolarized, the influx of calcium is restricted, potassium conductance increases, and there is a decrease in the subsequent release of excitatory neurotransmitters from the first synaptic axon.[40] Baclofen reduces the excitability of primary afferent

Table 2. DRUGS APPROVED FOR THE TREATMENT OF SPASTICITY

Generic Name	Commercial Name	Comment	Tablet Strength (mg)
Baclofen	Lioresal	$GABA_b$ agonist	10 or 20
Tizanidine	Zanaflex	α_2-Agonist	4
Diazepam	Valium	Benzodiazepine	5 or 10
Dantrolene sodium	Dantrium	Excitation/contraction uncoupled	25 or 100

GABA = γ-aminobutyric acid.

terminals, enhances presynaptic inhibition, inhibits mono- and polysynaptic reflex activity, reduces gamma motor neuron activity, and reduces muscle spindle sensitivity.[89]

Baclofen is effective in an oral dose and mainly is eliminated from the body unchanged through the kidney, although 15% is metabolized in the liver. In patients with impaired renal function, the dosage should be reduced. It is recommended that liver function parameters should be tested prior to initiating baclofen therapy, with a periodic re-examination of these parameters during baclofen therapy. Because one of the main side effects of baclofen treatment is sedation, the initial dose should be low and the dosage should be slowly titrated upward by adding 5 mg every 3 to 4 days. The recommended maximum dosage is 80 mg per day, given in four divided doses; there are reports, however, of improved therapeutic effects with safety at doses as high as 240 mg/day.[43, 82]

The most common adverse effects associated with baclofen treatment are sedation, drowsiness, and fatigue. Patients should be cautioned regarding the operation of automobiles or other machinery and about other activities made hazardous by decreased alertness. Baclofen also may produce dizziness, ataxia, hypotonia, weakness, paresthesia, and mental confusion. In a group of ambulatory multiple sclerosis patients baclofen has been reported to cause deterioration in walking ability.[33] Although baclofen is a GABA agonist, it can have a paradoxical proconvulsant effect, though such an occurrence is rare. Baclofen should not be discontinued abruptly because of the risk of withdrawal seizures, confusion, hallucinations, and rebound muscle spasticity with fever.

Tizanidine (Zanaflex)

Tizanidine is an imidazoline derivative and, like the related α_2-adrenergic agonist clonidine, binds to both α_2-adrenergic and imidazoline receptor sites, both spinally and supraspinally.[65, 78, 86] In the spinal transected cat, tizanidine has been shown to decrease reflex activity, especially polysynaptic reflex activity.[20] This finding has been corroborated by the observation that tizanidine has an antinociceptive effect in animal models.[21, 22, 41] Tizanidine, like clonidine, may restore or enhance noradrenergic presynaptic inhibition in spastic patients. Several European and American studies have shown that tizanidine is safe and equal in effectiveness to baclofen and diazepam, but with a favorable tolerability profile. One trial in which muscle strength was carefully tested in a variety of spastic patients showed improvement during tizanidine treatment.[44]

Tizanidine facilitates vibratory inhibition of the H-reflex, associated with clinically useful antispasticity effects in patients.[23] These observations are similar to those seen with clonidine.[65] The dosage of tizanidine producing antispasticity effects is less sedating than diazepam or baclofen, and they are manifest without inducing muscle weakness.[44, 62] Tizanidine is tolerated well and beneficial in treating spasticity of various

etiologies.[30] Tizanidine does not induce a consistent lowering of blood pressure or pulse as clonidine does.[12] Symptomatic hypotension, however, has been reported when tizanidine is taken with an antihypertensive drug; therefore, the concomitant administration of tizanidine and antihypertensive drugs should be done carefully.

Tizanidine is absorbed well after an oral dose with extensive first pass hepatic metabolism to inactive compounds that are subsequently eliminated in the urine. Therefore, tizanidine should be used with caution in patients with known liver abnormalities. Because the most common side effects reported during the clinical trials with tizanidine include dizziness and drowsiness, the authors recommend beginning tizanidine therapy with a single dose of 2 to 4 mg at bedtime. Dosage increases of 2 to 4 mg every 2 to 4 days are recommended; most clinicians experienced with tizanidine, however, recommend a slow and gradual upward titration, particularly for multiple sclerosis patients. Titration of tizanidine should be tailored to the patient and the maintenance dosage is the one at which the therapeutic goals have been met with the least side effects. The maximum recommended dosage is 36 mg per day.

Benzodiazepines

In general, the effects of benzodiazepines are mediated by a functionally coupled benzodiazepine-GABA receptor chloride ionophore complex.[69, 80] The clinical effectiveness of the benodiazepines varies and may be related to the existence of both high- and low-affinity benzodiazepine receptors as well as their duration of action (Table 3). The relative length of action is related to the duration of activity and rate of metabolism of the parent compound as well as the production and elimination of pharmacologically active metabolites. Diazepam, chlordiazepoxide, and clonazepam are considered to be long-acting benzodiazepines, whereas oxazepam, alprazolam, and lorazepam are considered to be short-acting without significant production of active metabolites. Generally, benzodiazepines cross the placental barrier and are secreted in breast milk. The benzodiazepines are metabolized extensively, mostly by the microsomal enzymes of the liver.

Diazepam (Valium)

Diazepam is a benzodiazepine that suppresses behavioral arousal, agitation, or anxiety. It reduces polysynaptic reflexes and has muscle relaxant, sedative, and antispasticity effects.[24, 57, 71, 81] Commonly, diazepam therapy is initiated with a bedtime dose of 5 mg, increasing to 10 mg as needed. Diazepam is absorbed well after an oral dose. Peak blood level occurs in 1 hour. It is metabolized to active compounds N-desmethyldiazepam (nordiazepam) rather then oxazepam. The half-life of diazepam (including active metabolites) is 20 to 80 hours, and it

Table 3. BENZODIAZEPINES

Generic Name	Commercial Name	Comment	Tablet Strength (mg)
Long-acting			
Chlordiazepoxide	Librium	Long acting anxiolytic	10
Clorazepate	Tranxene	1,4-benzodiazepine agonist	3.75, 7.5
Diazepam	Valium	1,4-benzodiazepine agonist	5, 10
Flurazepam	Dalmane	Long acting sleep induction	15, 30
Intermediate-acting			
Alprazolam	Xanax	Anxiolytic-antipanic	0.5, 1, 2
Bromazepam	Lectopam	Anxiolytic-sedative	1.5, 3, 6
Clobazam	Frisium	1,5-benzodiazepine agonist	10
Clonazepam	Rivotril or Klonopin	1,4-benzodiazepine agonist	0.5, 2
Lorazepam	Ativan	Sleep induction/maintenance	0.5, 1, 2
Nitrazepam	Nitrazadon	Hypnotic-anticonvulsant	5, 10
Oxazepam	Serax	Sleep induction/maintenance	10, 15, 30
Temazepam	Restoril	Sleep induction/maintenance	15, 30
Tetrazepam	Myolastin	Available in Russia	???
Short-acting			
Midazolam	Versed	Imidazo-benzodiazepine agonist	N/A
Triazolam	Halcion	Short-acting sleep induction	0.25

is 98% to 99% protein bound. The significance of the protein binding is that in patients with low serum albumin, such as is often the case in spinal cord injured and stroke patients, the incidence of undesirable sedation is increased. Daytime therapy is initiated with 2 mg and increased as needed.

The signs of diazepam intoxication are somnolence progressing to coma. Although benzodiazepines generally are regarded to have a wide margin of safety, the rate of fatal benzodiazepine poisoning in Britain over a decade was found to be 5.9 per million prescriptions.[81] Near term infants born with benzodiazepine intoxication are at particular risk. A 22-year-old, who was 36 weeks pregnant, consumed 250 to 300 mg of diazepam. She was somnolent but responsive. The fetal heart rate showed decreased variability and absence of accelerations. The benzodiazepine antagonist flumazenil 0.3 mg was given to the mother intravenously. Within 5 minutes, behavioral arousal in the mother and improved fetal heart rate variability were observed.[84]

Symptoms of withdrawal from high dose diazepam (> 40 mg per day) include anxiety and agitation; restlessness; irritability; tremor; muscle fasciculation and twitching; nausea; hypersensitivity to touch, taste, smell, light, and sound; insomnia; nightmares; seizures; hyperpyrexia; psychosis; and possibly death. The intensity of the symptoms, and hence the risk of death, is related to the prewithdrawal dose. Symptoms of withdrawal from low dose diazepam (< 40 mg per day) are more likely if the patient has taken the drug consistently for more than 8 months.

For a long-acting benzodiazepine like diazepam, onset of these symptoms occurs 2 to 4 days after the drug is stopped, 1 to 2 days for short-acting benzodiazepines. Withdrawal symptoms may persist for 6 months, even when the benzodiazepines are withdrawn slowly over 4 to 6 weeks.[34]

Clonazepam (Klonopin, Rivotril)

Clonazepam is indicated for the suppression of myoclonic, akinetic, or petit mal seizure activity, alone or as an adjunct. It is absorbed well after an oral dose, with maximum blood concentrations occurring in 1 to 2 hours. It is 98% bioavailable, with <1% excreted in the urine. Eighty-six percent is bound in plasma. Clonazepam is a cytochrome P 3A substrate. It has a 7-amino metabolite, and the half-life of clonazepam is 18 to 28 hours. Clonazepam is used in spasticity mainly to suppress nocturnal spasms that disturb sleep. It is prescribed most commonly as 0.5 to 1 mg at night. For patients who find morning sedation excessive, the tablet can be broken in half and 0.25 mg taken at night.

Clorazepate Dipotassium (Tranxene)

Clorazepate is a pro-drug for desmethyldiazepam and is rapidly decarboxylated to this form in gastric juice. Clorazepate has been shown to have antispasticity effects in patients with multiple sclerosis, but no myotonolytic effect in patients with rigidity due to encephalopathy.[52] The half-life of clorazepate is 1 to 3 hours, but the half-life for desmethyldiazepam is as long as 106 hours.

Lorazepam (Ativan)

Lorazepam has an intermediate length of action as an anxiolytic and sedative, and is conjugated to an inactive metabolite independent of hepatic microsomal oxidation. The peak plasma concentration after a sublingual dose of lorazepam occurs in approximately 60 minutes.

Ketazolam (Loftran)

Because ketazolam is a long-acting benzodiazepine like diazepam, the market for this pharmaceutical was not sufficient, so it is no longer available in Canada. It was found to be comparable to diazepam in a global comparison of antispasticity effectiveness.[5]

Clobazam (Frisium)

Clobazam is a 1,5-benzodiazepine with anticonvulsant properties that has not been reported as a treatment for spasticity. It is likely that the differences observed between clobazam and the 1,4-benzodiazepines is the variation of agonist action at the high affinity benzodiazepine receptor. It is absorbed well after an oral dose and reaches peak plasma

concentration in 1 to 4 hours. Clobazam is metabolized extensively to a number of active metabolites, N-desmethylclobazam being the most important. The half-life of clobazam is 10 to 30 hours, 36 to 46 hours for N-desmethylclobazam, and both increase with the age of the patient. Clobazam is available as a scored 10 mg tablet. The recommended daily anticonvulsant dose for adults is 5 to 15 mg per day, and can be given in divided doses or as a single nighttime dose. The recommended maximum dose is 80 mg, and one should periodically monitor liver function tests, as with all benzodiazepines.

Midazolam (Versed)

Typically used as an adjunct for anesthesia, midazolam is not used currently as a treatment for spasticity because of its intravenous formulation and the profound state of amnesia produced by this benzodiazepine. Recently, it has been reported, however, to be useful as a pre-treatment for children receiving botulinum toxin injections. The midazolam solution is mixed with a sweet tasting fluid and given orally. Because midazolam can cause significant impairment of oxygenation, oxygen saturation and vital signs should be monitored constantly. The available concentrations are 1 and 5 mg/mL. Published pharmacokinetic data relating to intramuscular or intravenous administration show that midazolam and its active metabolite, 1-hydroxymethyl midazolam, have a short half-life of 1 to 2.8 hours each.

Dantrolene Sodium (Dantrium)

Dantrolene sodium is a hydantoin derivative whose primary pharmacologic effect is to reduce calcium flux across the sacroplasmic reticulum of skeletal muscle. This action uncouples sarcolemmal excitation and skeletal muscle contraction.[39, 93] The oral formulation is prepared as a hydrated sodium salt to enhance absorption (approximately 70%), which occurs primarily in the small intestine. After a dose of 100 mg, the peak blood concentration of the free acid, dantrolene, occurs in 3 to 6 hours, and the active metabolite, 5-hydroxydantrolene, occurs in 4 to 8 hours. Dantrolene sodium has been shown to produce a dose-dependent decrease in the stretch reflex[39] and grip strength.[32] Dantrolene is lipophilic and crosses cell membranes well, achieving wide distribution and significant placental concentration in the pregnant patient. Liver metabolism by mixed function oxidase and cytochrome P-450 produces 5-hydroxylation of the hydantoin ring and reduction of the nitro group to an amine, which is then acetylated. Urinary elimination of 15% to 25% of the unmetabolized drug is followed by urinary excretion of the metabolites after oral administration. Median elimination half-life is 15.5 hours after an oral dose, and 12.1 hours after an intravenous dose.

The majority of placebo controlled clinical trials of dantrolene have shown a reduction of muscle tone, tendon reflexes and clonus, and increased passive motion.[72] There have been mixed conclusions regarding the effects of dantrolene sodium on gross motor performance and strength. In comparative trials with spasticity of different etiologies, some have suggested that the best responders to dantrolene sodium are stroke patients, whereas others suggest that spinal cord injured patients improve most. Most investigators agree, however, that patients with multiple sclerosis generally do not benefit from dantrolene treatment.[72] In four trials of children with cerebral palsy, dantrolene sodium was found to be superior to placebo. The degree of improvement appeared greater in children than adults. One study found dantrolene to be superior to baclofen; another suggested efficacy equal to diazepam.[93] In addition to its antispasticity effects, dantrolene has been reported to be useful in the treatment of hyperthermia following abrupt baclofen withdrawal,[42, 55] in malignant hyperthermia,[32] and in the neuroleptic malignant syndrome.[93]

Hepatotoxicity is a significant concern with using dantrolene sodium. In a large cohort analysis of patients receiving dantrolene sodium for more than 2 months, the overall incidence of hepatotoxicity is reported to be 1.8%, symptomatic hepatitis occurring in 0.6%, and fatal hepatitis in 0.3%, with the greatest risk in females older than 30 years of age, taking more than 300 mg/day for more than 60 days.

Initiation of antispasticity treatment with dantrolene sodium should begin with 25 mg once daily, increasing every 4 to 7 days by 25 mg increments to a maximum of 100 mg 4 times per day. The dosage at which the anticipated therapeutic response occurs with least side effects should be the maintenance dose.

APPROVED "MUSCLE RELAXANTS"

Cyclobenzaprine (Flexeril)

Cyclobenzaprine is related structurally and pharmacologically to the tricyclic antidepressants. It is a "centrally acting" muscle relaxant approved for use in "localized muscle spasm" of varying etiology. This description is meant to convey that cyclobenzaprine is not intended to be a treatment for spasticity associated with a central nervous system (CNS) disorder, but rather it is thought more correctly to be a treatment for muscle "spasm." It was not found to be an effective treatment for psychiatric conditions, Parkinson's disease, or spasticity associated with cerebral or spinal cord disease in children or adults, but it was better than placebo in reducing painful back spasms.[67] The usual adult dosage is 10 mg (one tablet) 3 times per day. Like other tricyclic antidepressants, cyclobenzaprine has anticholinergic side effects: dry mouth, blurred vision, increased intraocular pressure, urinary retention, and constipation. It is contraindicated in patients with cardiac abnormalities and in patients taking monoamine oxidase inhibitors.[92] Cyclobenzaprine should be used cautiously in patients with a history of psychiatric illness, with case reports of acute manic psychosis occurring during treatment.[6] Se-

vere overdose (900 mg) has been successfully treated intravenously with physostigmine (1 mg) (Table 4).[50]

Carisoprodol (Soma)

Carisoprodol, the isopropyl precursor of meprobamate, is a "centrally acting" muscle relaxant, whose antispasticity effects were tested by the then newly described Ashworth scale in 1964.[3] In that trial of 24 multiple sclerosis (MS) patients, 1 patient was much improved, 16 improved, 2 slightly improved, and 5 showed no change. Sedation and drowsiness are the main side effects; meprobamate dependence, however, is a significant clinical problem.[51] Chesrow et al suggest that carisoprodol is an effective treatment for muscle cramps.[16] The usual adult dosage is 350 mg (one tablet) 4 times per day. Severe withdrawal symptoms include agitation, restlessness, anorexia, vomiting, hallucinations, seizures, and, rarely, death.[92]

Chlorzoxazone (Paraflex)

Chlorzoxazone is a benzimidazole with central inhibitory properties, but is limited by low potency; hence, it has not been shown to be superior to placebo.[26] The usual adult dosage is 250 to 750 mg 3 or 4 times per day. Liver toxicity and two reported deaths due to hepatic failure suggest that this agent is contraindicated in patients with liver disease, and patients treated with chlorzoxazone should be monitored by liver function tests.[74]

Methocarbamol (Robaxin)

Methocarbamol is a carbamate analog derivative of mephenesin, designed to be longer acting and retain the inhibiting action on polysynaptic reflexes.[26] Methocarbamol is produced in 500- and 750-mg tablets. The usual adult dosage is 1000 mg 4 times per day.

Table 4. OTHER CENTRAL MUSCLE RELAXANT DRUGS

Drugs	Onset	Duration	Half-life
Carisoprodol	30 min	4-6 hours	8 hours
Chlorphenesin	30 min	5-10 hours	2.5-5 hours
Chlorzoxazone	1 hour	3-4 hours	1-2 hours
Cyclobenzaprene hydochloride	1 hour	4-6 hours	2-3 hours
Metaxolone	30 min	2-4 hours	1-2 hours
Methylcarbamol	1 hour	3-4 hours	14 hours
Orphenadrine	1 hour	12-24 hours	1-3 days

Data from Waldman HJ: Centrally acting skeletal muscle relaxants and associated drugs. J Pain Symp Management 9:434-441, 1994.

Orphenadrine Citrate (Norflex)

Orphenadrine citrate is an analog of the antihistamine diphenhydramine (Benadryl), and has shown some efficacy as an antispasticity treatment in SCI patients when given as an intravenous infusion.[13] The usual adult dosage is 100 mg twice per day. It has anticholinergic properties, and rare cases of aplastic anemia have been reported as an adverse reaction to this drug. A related compound, orphenadrine hydrochloride (Disipal), is a treatment for Parkinson's disease. Patch clamp and binding studies have revealed that orphenadrine is an uncompetitive *N*-methyl-D-aspartate (NMDA) type glutamate antagonist.[46]

Chlorphenesin Carbamate (Maolate)

Chlorphenesin carbamate is an agent that selectively inhibits the interneurons of polysynaptic pathways in the spinal cord, and α and γ motor neurons, by producing slight hyperpolarization and prolongation of the refractory period.[1] Chlorphenesin has been shown experimentally to have a dose dependent antinociceptive effect in adjuvant induced arthritis in the rat.[68] In experimental myelopathy in the dog, the *F*-wave was shown to decrease in duration with chlorphenesin treatment, suggesting that this drug does in fact have a central antispasticity effect.[53] Clinically this drug has been used in the treatment of painful neuralgia.[19] Chlorphenesin carbamate is available as 400 mg tablets. The usual dosage is 1 tablet 4 times a day, with the recommended maximum of 2400 mg per day. The principal side effect noted with chlorphenesin is drowsiness.

Metaxalone (Skelaxin)

The main effects of metaxalone were studied in a double blind study of 200 low back pain patients; a higher percentage of treated patients improved their range of motion and had less palpable muscle spasm than those receiving placebo.[31] The most frequently reported side effects were nausea, vomiting, dizziness, polyuria, headache, and, paradoxically, muscle cramps.[36] Hemolytic anemia and impaired liver function have been reported; therefore, monitoring of the red blood cell count and liver enzymes is advised. Metaxalone is supplied as 400 mg tablets. The usual dosage is 800 mg 3 or 4 times per day.

AVAILABLE PHARMACEUTICALS WITHOUT APPROVED ANTISPASTICITY INDICATION

Clonidine (Catapres, Dixarit, Catapressan)

The mechanism by which clonidine produces any of its many pharmacologic effects remains speculative. For example, clonidine reduces the discharge rate of locus coeruleus neurons, thereby decreasing tonic facilitation on sympathetic preganglionic fibers which would lower blood pressure and heart rate, but this effect appears to be specific to hypertensive individuals.[45, 85] Clonidine also has a spinal site of action that is α_2 selective.[88] With regard to its antispasticity effect, clonidine has been shown to produce marked inhibition of the short latency α-motoneuron response to group II muscle afferent stimulation in the spinalized cat, perhaps by augmenting presynaptic inhibition.[79] The antispasticity effect, however, like that of its antihypertensive effect, can be reversed by desipramine, which indicates that clonidine is likely to have a spinal as well as supraspinal site of action.[65] Clonidine treatment in SCI humans has been consistent with enhancement of α_2 mediated presynaptic inhibition of sensory afferents.[27, 64] Clonidine is 95% bioavailable after an oral dose; 62% is excreted in the urine, and its half-life is 5 to 19 hours. Because some patients may be very sensitive to the effects of clonidine, initial dosage should be low. The 25 μg formulation, available in Canada (Dixarit), can be taken orally twice per day to begin treatment. The dose can be increased every 3 days by 1 tablet per day as a 3 or 4 times per day dosage regimen. Alternatively, clonidine is available in the United States as a transdermal patch with two dosage formulations: 0.1 mg or 0.2 mg per day, which has been reported to be a useful treatment for spasticity.[94] The patch is designed to deliver the indicated amount of clonidine daily for 7 days. Blood pressure and pulse rate should be monitored periodically during treatment, as bradycardia and hypotension are common side effects of clonidine. Additional side effects are dry mouth, ankle edema, and depression.

Cyproheptadine (Periactin)

Cyproheptadine has been used safely for more than 20 years in the treatment of itching associated with hives, vascular headache, and anorexia; it is a histamine, acetylcholine, and serotonin antagonist. It also has been used in the treatment of repetitive spontaneous abortion. Cyproheptadine has been reported to decrease clonus in people with spasticity because of SCI or MS.[4] In patients whose gait is limited by clonus, cyproheptadine normalizes muscle firing patterns and increases walking speed.[91] In a comparative clinical trial, cyproheptadine had similar antispasticity efficacy to clonidine and baclofen in spinal cord injured patients.[63]

Cyproheptadine is available in 4-mg tablets. Treatment should be initiated as 4 mg at bedtime, increasing by a 4 mg dose every 3 to 4 days. The most commonly effective and tolerable dose is 16 mg in divided doses, such as 4 mg 4 times per day. The maximum recommended dose is 36 mg per day.

Chlorpromazine (Thorazine, Largactil)

Chlorpromazine, a well known sedative/antipsychotic, depresses the monosynaptic reflex to a greater extent than polysynaptic reflexes.[8, 18] In an open clinical trial, resting muscle tone decreased with chlorpromazine treatment. Adverse effects include sedation and the potential risk of tardive dyskinesia.

Riluzole (Rilutec)

Riluzole is an approved putative treatment for amyotrophic lateral sclerosis (ALS). It reportedly blocks the action of voltage sensitive sodium channels, thereby preventing release of excitatory aminoacids, and is associated with a reduction in stiffness associated with ALS.[7]

Cannabis (Cesamet, Marinol)

Over 4000 years ago, the ancient Chinese used the leaves of the cannabis sativa plant for medicinal purposes. The main active alkaloid is delta-9-tetrahydrocannabinol (THC), available as a prescription pharmaceutical dronabinol (Marinol), or the synthetic cannabinoid nabilone (Cesamet). The clinical indications for dronabinol and nabilone are nausea related to chemotherapy treatment. In 1842, O'Shaughenessy reported the use of hemp extract to treat muscle spasms associated with tetanus.[70] In 1890, Reynolds described the toxic effects and therapeutic use of cannabis in the treatment of epilepsy, chorea, and nocturnal spasms.[77] Anecdotal reports by patients with spasticity because of MS or SCI suggest that smoking marijuana has a muscle relaxing effect.[17, 28, 54] In a trial of 13 patients with MS, only five completed the trial, three taking 7.5 mg, one each taking 10 mg and 15 mg of THC, where the antispasticity effects and side effects appeared to be dose related.[87] Dronabinol, after an oral dose, is 4% to 12% bioavailable, less than 1% is excreted through the urine, and 95% of the drug is bound to plasma proteins. The half-life is 20 to 44 hours. It is formulated as 2.5 mg, 5 mg, or 10 mg capsules. Nabilone is formulated as a pulvule containing 1 mg, with a recommended dose of 1 to 2 mg twice per day.

APPROVED ANTICONVULSANTS

Gabapentin (Neurontin)

Gabapentin (1-[aminomethyl] cyclohexanazcetic acid) is an anticonvulsant that is structurally similar to GABA, but whose pharmacologic actions differ markedly; it crosses the blood-brain barrier, does not activate GABA receptors, and does not alter GABA metabolism. Gabapentin (GBP) is moderately well-absorbed after ingestion, with approximately 60% bioavailability after an oral dose of 300 mg, with a peak plasma concentration in 2 to 3 hours.[90] Higher individual doses have a progressively reduced bioavailability; after a dose of 1600 mg, the bioavailability is 35%.[10] The presence of food, however, does not alter absorption, but aluminum or magnesium hydroxide may reduce absorption by up to 20%. The elimination half-life is independent of dose and is 5 to 7 hours, on average. Gabapentin is not metabolized. It is eliminated by renal excretion or hemodialysis. The dosage should be limited in individuals with impaired renal function regardless of age.

In a trial of 15 multiple sclerosis patients given 1200 mg/day of gabapentin, significantly greater improvements in spastic muscle tone (total Ashworth score) and pain (Visual Faces Score) were observed relative to the placebo treatment condition.[61] Two studies suggest that a higher dosage of GBP may be needed for spinal cord injured patients (2400 to 3600 mg/day) to show antispasticity effects in terms of a change in the Ashworth Scale or brain motor control assessment, a new quantified method of tone evaluation.[37, 76] Encouraging results also have been reported regarding the use of GBP in a recent open-labeled trial among patients with hemifacial spasm. Responses were dose-related, with better responses consistently observed among patients receiving greater than 1200 mg/day.[56]

Vigabatrin (Sabril)

Vigabatrin, γ-vinyl GABA (4-amino-hex-5-enoic acid), is a GABA analog that irreversibly inhibits the activity of GABA transaminase. Vigabatrin is absorbed well after an oral dose, and the peak plasma concentrations occur within 2 hours. It is widely distributed in the body and eliminated mainly by the kidney.

In two controlled trials, the antispasticity efficacy of vigabatrin treatment was superior to placebo and similar to baclofen in adult patients with spasticity of spinal origin.[35] The plasma half-life is 5 to 8 hours in young adults, and 12 to 13 hours in the elderly. The initial starting dose of vigabatrin is 500 mg twice per day, and is often quite sedating. It is availible as a 500 mg tablet or a granular powder that can be dissolved in water, milk, or juice immediately before oral administration.

Valproate (Depakene)

Valproic acid (VPA) has been suggested as a treatment for stiff-man syndrome.[29] VPA is useful for the treatment of myoclonus.[59, 75]

Thyrotropin Releasing Hormone (L-pyroglutamyl-L-histidyl-L-prolinamide)

In addition to the localization of thyrotropin-releasing hormone (TRH) and TRH receptors within the spinal cord, a number of observations are consistent with the notion that TRH plays an important role as a neuromodulator involving spinal cord neuronal excitability.[95]

L-Threonine

L-threonine is an aminoacid precursor to glycine, an important inhibitory neurotransmitter. In a double blind, placebo controlled, crossover, add-on designed study of 33 spastic patients, dry L-threonine power was encapsulated in 500 mg doses and given as 6 grams per day in three divided doses. Side effects were minimal and a modest, but definite reduction in the Ashworth score was noted.[49]

N-METHYL-D-ASPARTATE ANTAGONISTS

With the recent cloning of the NMDA receptor, there are now identified multiple NMDA receptor subtypes.[60] The antagonists for these receptor subtypes have been shown to have a number of beneficial properties, among them neuro-protective effects, analgesia, and possibly muscle relaxation. Among these compounds are MK-801, the polyamine spider toxin argio toxin, isenprodil, dextrorphan, dextromethorphan, memantine, and amantadine (Symmetrel).[66]

Memantine (1-amino-3,5-dimethyladamantane)

This drug has anticonvulsant properties and has been used to treat Parkinson's disease and dementia.[2, 25, 48] Memantine, through microdialysis experimentation, produces a dose dependent and significant increase in extracellular dopamine release and metabolism in the prefrontal cortex and striatum, which is similar in magnitude to amphetamine (and similarly inhibits binding of the NMDA antagonist, MK-801).[83]

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Treatment of Spasticity With Botulinum Toxin

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Abstract:

Spasticity is an abnormal increase in muscle contraction often caused by damage to central motor pathways that control voluntary movement. During clinical examination, spasticity manifests as an increase in stretch reflexes, producing tendon jerks and resistance appearing as muscle tone. There are many causes of spasticity, including demyelination from multiple sclerosis, congenital damage from diseases such as cerebral palsy, trauma to the brain or spinal cord, hemorrhage or infarction, and other pathologic conditions that interrupt neural pathways. Effects of spasticity range from mild muscle stiffness to severe, painful muscle contractures and repetitive spasms that reduce mobility and substantially impede normal activities of daily living. Botulinum toxin therapy reduces spasticity and pain associated with several disorders. Local treatment with botulinum toxins can be used as adjunctive therapy, along with oral antispasticity medications, or alone to provide localized decrease in symptoms of spasticity and pain. Botulinum toxin therapy may be particularly useful for patients with spasticity due to stroke, whose treatment can be tailored based on recovery of function over time. In addition, botulinum toxin therapy is safe for pediatric patients, including children with cerebral palsy, who may not be able to tolerate the cognitive side effects of oral medications. Results of studies evaluating botulinum toxin for the treatment of spasticity due to various causes are presented here.

Key Words: Spasticity—Neural pathways—Demyelination—Botulinum toxin

Spasticity is defined as a velocity-dependent increase in tonic stretch reflexes and is one component of the upper motor neuron syndrome. Common causes of spasticity include demyelination from multiple sclerosis, congenital damage from cerebral palsy, trauma to the brain or spinal cord, stroke, and hereditary spastic paraparesis. Spasticity can be described as having "negative" and "positive" symptoms. Negative symptoms include decreased coordination, loss of dexterity, muscle weakness, and fatigue. These are usually managed with physical therapy and the use of assistive devices. The positive symptoms manifest clinically as hypertonicity, exaggerated deep tendon reflexes, muscle spasm, persistence of primitive reflexes, clonus, extensor plantar responses, and discordant mass activation of muscles. It is the positive attributes of spasticity that are treated with pharmacologic and surgical intervention.[1,2]

Effects of spasticity range from mild muscle stiffness to severe painful muscle contractures and repetitive spasms that reduce mobility and substantially impede activities of daily living. Some patients (particularly those with brain or spinal cord injury) suffer with disabling pain related to injury of sensory pathways in cord or brain or to musculoskeletal distortion from focal muscle overactivity. Spasticity may be transient, after recovery from trauma, or chronic, especially when associated with diseases such as cerebral palsy. When spasticity is caused by an injury, muscles may still stretch normally in response to stimuli. This type of spasticity is described as phasic. Over time, however, decreasing muscle stretch can lead to permanent contractures, or tonic spasticity. Prolonged contracture can result in posture and joint deformities. Early intervention is critical to preserve as much normal muscle reactivity as possible.

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The effects of spasticity on clinical function vary widely from one patient to another; treatment decisions can therefore be quite complex.[3] In some cases, spasticity may not require treatment. For example, a patient with minimal voluntary control of his legs but prominent extensor tone of lower extremities may use his spasticity to help in ambulation or transfer. In a different scenario, a patient with poor cognition who would not be fully aware of benefit may be treated to facilitate caregiving.[4] Treatment may be initiated to relax muscles to improve the fit of an orthotic device such as a brace. For painful spasticity, the potential source(s) of pain should be identified (if possible) and treated accordingly. Importantly, the approach to treatment should be based on individual goals for improving function, including mobility and range of motion, and decreasing pain and frequency of muscle spasm.

TREATMENT OF SPASTICITY

Treatment of spasticity usually involves a multidisciplinary approach. Decreasing nocioceptive stimuli, such as pain or cold, that can trigger symptoms is the first step in reducing the frequency of transient spasticity.[2,4] Physiotherapy to stretch muscles and prevent muscle shortening is standard in spasticity management. Oral antispasticity agents, such as benzodiazepines, dantrolene, tizandine, oral baclofen, and several other classes, can be effective for a generalized reduction in body tone but can produce significant adverse effects, ranging from sedation to serious hepatotoxicity.[5,6] In addition, efficacy tends to diminish with prolonged use, necessitating higher doses and increasing the risk for adverse effects. Sedation, muscle weakness, dizziness, and other common side effects of oral antispasticity drugs can complicate the patient's efforts to improve function and may not be appropriate for some populations, such as children. Chemodenervation with phenol or botulinum toxin injection may be useful for controlling focal spasticity in some patients. For severe generalized spasticity that has not responded to more conservative approaches, intrathecal baclofen or surgery may provide relief for selected patients.

CHEMODENERVATION WITH BOTULINUM TOXIN

Chemodenervation with phenol or botulinum toxin injection can effectively reduce harmful spasticity in one area while preserving useful motor function in another.[7] Phenol is administered by motor point or nerve point blockade and works by denaturing proteins, resulting in neural tissue dysfunction. Axon recovery usually occurs, but higher concentrations of phenol (5% solution) may produce permanent injury.[8] Phenol injection also can cause lethargy, nausea, and pain and dysesthesia from nerve tissue necrosis.[2] Botulinum toxin is administered by IM injection and produces dose-related weakness of affected muscles by inhibiting the release of ACh at the neuromuscular junction. Botulinum toxin is gaining rapid acceptance for spasticity because of its efficacy, ease of administration, and lack of significant adverse effects.[2,7]

Two antigenically distinct serotypes of botulinum toxin, type A and type B, are commercially available. These include two different formulations of Type A: Botox (Allergan, Inc., Irvine, CA) and Dysport (available in Europe only; Ipsen, Ltd., Berkshire, UK). Both are effective, but the dose equivalency is approximately 300–500 U of Dysport to 100 U of Botox. Type B is available as Myobloc in the United States and NeuroBloc in Europe (Elan Pharmaceuticals, San Diego, CA). A simple dose conversion between botulinum toxin serotypes (e.g., type A with type B, or vice versa) is not recommended because each serotype has unique pharmacologic properties. Clinical trials have confirmed the effectiveness of both type A and type B in a variety of neurologic disorders characterized by excessive or inappropriate muscle contraction.[9–12] In addition, pain reduction is another benefit of botulinum toxin therapy, particularly in patients with cervical muscle contraction. It has been suggested that that botulinum toxin may alleviate pain through mechanisms other than simple muscle weakening.

Kirazli et al.[7] conducted one of the first studies to compare botulinum toxin and phenol in the treatment of spasticity. In this randomized, double-blind study, 20 patients with post-stroke spasticity were randomly assigned to receive either 400 U of botulinum toxin type A injected into the calf muscles or a tibial nerve blockade with 3 ml of 5% phenol. Patients were evaluated at baseline and at weeks 2, 4, 8, and 12. At follow-up, both treatment groups showed significant improvement in Ashworth Scores for dorsiflection. However, scores for eversion and ambulation were improved significantly only in type A-treated patients. Moreover, Global Assessment Scores and active and passive range of motion scores were better in patients treated with type A versus phenol. Botulinum toxin and phenol injections were both effective in reducing lower limb spasticity in post-stroke patients. However, functional improvements were better overall with toxin therapy.

CLINICAL TRIALS OF BOTULINUM TOXIN FOR SPASTICITY

Many studies have been conducted to evaluate the efficacy of botulinum toxin for the treatment of spasticity

and to determine its clinical role. Some studies consist of a heterogeneous patient population with spasticity attributed to different etiologies, whereas others evaluate a single defined group of patients with spasticity due to a specific cause, such as multiple sclerosis (MS), cerebral palsy, stroke, or traumatic injury. When evaluating the appropriate use of toxin therapy, clinicians should consider the condition for which spasticity is being treated. For example, patients with MS often face morbidity from many types of symptoms in addition to spasticity. Pediatric patients with cerebral palsy may require special considerations with regard to body size and the chronic long-term nature of their disease. Patients with spasticity due to stroke or to brain or spinal cord injury face lengthy recovery times and may require flexible treatment regimens that can be tailored to their specific patterns of spasticity. Some of the more important studies that evaluate botulinum toxin for spasticity are reviewed below.

Heterogeneous populations

Several retrospective and open-label studies evaluating botulinum toxin for upper and/or lower limb spasticity in heterogeneous populations have been published and, in general, show positive results with botulinum toxin treatment. One long-term retrospective case study reviewed 13 patients with spasticity due to cerebral palsy, multiple sclerosis, or traumatic brain injury who were treated with botulinum toxin type A (Dysport) for 3 years. All patients with cerebral palsy and one patient with traumatic brain injury were children. Seven patients received physical therapy and three received oral antispasticity drugs concomitantly. Results were classified as good if identified treatment goals were achieved and maintained for 3 months or more, or as moderate for benefits ranging from 2 weeks to just less than 3 months. Lack of response at 2 weeks was classified as a poor result. Dosing for adults was determined on the basis of the size of the muscle treated and the severity of spasticity. Dosing for children was based on body weight. Patients were evaluated every 3 months for the 3-year study period. Repeat injections were administered to the same muscle sites each time. A total of 38 injections were administered, with 10 given in upper limb muscles. The mean dose of type A administered to children was 177.3 U. For adults with upper limb spasticity, the mean dose was 230 U, and for lower limb spasticity 296 U. Treatment goals were achieved in 10 of 13 patients, with response rated as good in 100% of children and in 19% of adults. Results were moderate for 44% and poor for 38% of the remaining adults. Investigators concluded that treatment with type A was effective, particularly for children, who received larger proportional doses than adults. The limitations of this study include its small sample size, retrospective design, and concomitant therapy. Advantages noted with treatment using botulinum toxin included ease of administration, lack of skin sensory loss or dysesthesia associated with phenol blocks, and availability as outpatient therapy. Of particular note was the ease with which botulinum toxin was administered to children, as no anesthesia was required.[13]

Dunne et al.[14] evaluated type A (Dysport) treatment in 40 patients with chronic limb spasticity (upper, n = 13; lower, n = 27). The majority of patients had disabling limb posture and/or painful muscle spasms or painful and difficult passive stretches that were refractory to conventional therapies. Blinded, random review of videotapes of patient movements was used to assess spasticity and motor function. In addition to the Ashworth Spasticity Scale, several other objective scales were used to measure spasm frequency, motor skills, mobility, active and passive range of motion, and pain. Patients were assessed at two baseline visits and again 4 to 6 weeks after treatment. Type A was injected under electromyographic guidance (EMG). The mean total dose of type A administered was 175 U for upper limb spasticity, 221 U for a single lower limb, and 321 U for both lower limbs. After treatment with type A, 34 patients (85%) achieved beneficial effects. Range of motion improved for 31 patients, pain was reduced for 28 of 31 patients with pain at baseline, and function improved for 16 patients. The mean change in spasticity as measured by the Ashworth Spasticity Scale (0–4) was 1.2, a decrease from the baseline score of 3.2. Blinded videotaped assessment also showed improvement in passive range of joint motion in 30 patients. The six patients who did not respond significantly had no similar characteristics to explain their lack of response. Adverse effects occurred in 19 patients and included mild to moderate pain during injection (n = 19) and symptomatic weakness of injected muscles (n = 1).

More recently, a prospective open-label study of botulinum toxin type B (Type B; Myobloc) for treatment of limb spasticity was conducted.[15] Ten patients with arm or leg spasticity due to stroke, cerebral hemorrhage, traumatic brain injury, or spinal cord injury were enrolled. Spasticity, as measured by the Modified Ashworth Score (MAS), was 2 or higher on a scale of 0–4 for patients included in the study. Spasticity was present in the wrist, hand, or both for seven patients and in the ankle, foot, or both for three patients. Outcome measures were obtained at baseline and at weeks 4, 8, and 12 and included the MAS to assess spasticity and tone intensity, the Medical Research Council (MRC) assessment of muscle strength, range of motion (ROM), Spasm Frequency Scale (SFS), patient and investigator global assessments, patient pain

Visual Analog Scale (VAS), and treatment goal attainment. Muscle selection was based on clinical assessment and patient goals, and EMG guidance was used for localization. Doses administered ranged between 375 and 2,500 U for arm muscles and between 2,500 and 7,500 U for leg muscles. A reduction in spasticity and tone, as measured by a decrease in MAS of 1 to 2 points, was greatest for wrist and finger flexors at weeks 4 and 8. Reduction in mean MRC scores of approximately 0.5 points in treated muscles was observed at week 4. No significant weakness was reported in nontargeted muscles. At week 4, 45% of patients had attained their treatment goals. This declined to 25% at week 8 and 5% at week 12. Pain was significantly improved at weeks 4 and 8, and investigator and patient global assessments reported improvement at weeks 4 and 8. Adverse effects reported were transient and included one report each of dry mouth, flu-like symptoms, focal weakness, and fatigue. Investigators concluded that type B effectively reduced objective measures of spasticity without producing weakness. Doses of up to 10,000 U were safe and well-tolerated.[15]

An important benefit provided by treatment with botulinum toxin is pain reduction. A recent prospective study of 60 patients with spasticity-associated pain attributable to several conditions, ranging from stroke to cerebral palsy, found that treatment with botulinum toxin (Botox) provided relief of pain for the majority (90%). Results were comparable for patients with acute and chronic spasticity.[16] Additional discussion of the effects of botulinum toxin can be found elsewhere in this supplement.

It cannot be overemphasized that dosing units for botulinum toxin type A and type B differ and should not be quantified in terms of a ratio. Suggested dosing guidelines for Botox and Myobloc in upper and lower limb spasticity are presented in Table 1.[17,18] Importantly,

TABLE 1. *Dosing of botulinum toxin type A (Botox) and type B (Myobloc) for spasticity*[17,18]

	Muscles	Dose range type A (U)	Number of injection sites	Dose range type B (U)	Number of injection sites
Upper limb spasticity					
Adducted/internally rotated shoulder	Pectoralis complex	75–150	4	2,500–5,000	2–6
	Latissimus dorsi	50–150	4	2,500–5,000	2–6
	Teres major	25–75	1	1,000–3,000	1–4
	Subscapularis	25–75	1	1,000–3,000	1–2
Flexed elbow	Brachioradialis	25–75	2	1,000–3,000	2–4
	Biceps	50–200	4	2,500–5,000	2–4
	Brachialis	25–75	2	1,000–3,000	2
Pronated forearm	Pronator quadratus	10–50	1	1,000–2,500	1–2
	Pronator teres	25–75	1	1,000–2,500	1–2
Flexed wrist	Flexor carpi radialis	25–100	2	1,000–3,000	1–2
	Flexor carpi ulnaris	10–50	2	1,000–3,000	1–2
Thumb-in-palm	Flexor pollicis longus	5–25	1	1,000–2,500	1–2
	Adductor pollicis	5–25	1	500–2,500	1
	Opponens	5–25	1	500–1,500	1
Clenched fist	Flexor digitorum superficialis	25–75	4	1,000–3,000	1–2
	Flexor digitorum profondus	25–100	2	1,000–3,000	1–2
Intrinsic plus hand	Lumbricales interossei	10–50/hand	3	1,500–4,500	3
Lower limbs					
Flexed hip	Iliacus	50–150	2	3,000–7,500	2–3
	Psoas	50–200	2	3,000–7,500	1–2
	Rectus femoris	75–200	3	2,500–5,000	1–3
Flexed knee	Medial hamstrings	50–150	3	2,500–7,500	2–4
	gastrocnemius	50–150	4	3,000–7,500	2–4
	Lateral hamstrings	100–200	3	2,500–7,500	2–4
Adducted thighs	Adductor brevis/longus/magnus	75–300	6/leg	5,000–10,000	2–6
Stiff (extended) knee	Quadriceps mechanism	50–200	4	5,000–7,500	2–6
Equinovarus foot	Gastrocnemius medial/lateral	50–200	4	3,000–7,500	2–4
	Soleus	50–100	2	2,500–5,000	1–3
	Tibialis posterior	50–200	2	3,000–7,500	1–3
	Tibialis anterior	50–150	3	2,500–5,000	1–2
	Flexor digitorum longus/brevis	50–100	4	2,500–5,000	1–2
	Flexor hallucis longus	25–75	2	1,500–3,500	1–2
Striatal toe	Extensor hallucis longus	20–100	2	2,000–4,000	1–2

dosing regimens for patients with symptoms of spasticity should be determined on the basis of individual treatment goals and response to previous treatment.

Multiple sclerosis

Spasticity is a common symptom of MS. Because MS can produce so many different kinds of symptoms and the pattern of symptoms can be erratic, treating patients for spasticity and other symptoms at the same time can lead to complex medication regimens. An advantage of localized injection with botulinum toxin is the lack of systemic side effects for patients who are likely to be using a variety of medications. Additional advantages of using botulinum toxin to treat patients with MS were described in a 1993 pilot study evaluating its effectiveness in two patients with lower extremity spasticity. Borg-Stein et al.[19] noted that botulinum toxin could be used to target specific muscle groups in a graded manner to preserve useful spasticity that could aid the patient in remaining mobile or improving the ability to transfer. A common effect of spasticity in adductor muscles is interference with catheterization. In this early investigation of type A toxin, both patients had reduced spasticity, and one patient reported increased ease of abduction for catheterization. However, each patient also experienced reduction in tone in noninjected muscles.

Recently, Hyman et al.[20] published results of a multicenter prospective, randomized, double-blind, placebo-controlled study evaluating botulinum toxin type A (Dysport) at three different doses for treatment of disabling spasticity due to MS and involving the hip adductor muscles. A total of 74 patients were randomized to receive 500, 1,000, or 1,500 U of type A, or placebo injected into the hip adductor muscles. Spasticity was assessed at baseline and at weeks 2, 4, 8, and 12. Muscle tone and spasm frequency in each leg were assessed using the MAS. Patients and investigators were also asked to rate response to treatment at the completion of the study using a five-point scale (excellent to no benefit). Spasm frequency was reduced for all groups, but muscle tone was reduced only in the active treatment groups. Improved distance between the knees was significantly better for the 1,500 U group compared with placebo. Duration of benefit was longer for all type A treatment groups compared with placebo. Reduction in MAS was greatest for the 1,500 U group, as measured at week 4. Adverse events (particularly weakness) occurred most frequently in the highest dose group, but the overall incidence of adverse events between groups was not significantly different. Investigators concluded that administration of botulinum toxin type A provided benefit in reducing the degree of hip adductor spasticity associated with MS.[20]

Although ongoing study is needed to better characterize the use of botulinum toxin for the treatment of spasticity in patients with MS, a general consensus from the published literature to date is that treatment may contribute to improvements in maintaining hygiene, performing catheterization, sitting, transferring, and positioning. In addition to reducing muscle spasm and its associated pain, botulinum toxin may also improve bladder voiding for patients with hypertonia of the external sphincter.[21,22]

Cerebral palsy

The treatment of spasticity associated with cerebral palsy can be complicated by changes in patterns of muscle dysfunction as the child grows. Because cerebral palsy is a chronically debilitating disease, early treatment is desirable to improve gross motor function (i.e., specifically to preserve or improve the ability to walk) and to reduce contractures and delay corrective surgery.[23,24] For children with more severe disability, treatment goals often include relieving spasticity to improve or facilitate hygiene care and to relieve pain.[24]

Spastic equinus foot is a very common lower limb dysfunction in children with cerebral palsy. Botulinum toxin injected into the gastrocnemius muscle has been used successfully to improve gait and ankle range of motion and to delay corrective surgery for this condition.[25,26] Botulinum toxin injected into hamstring muscles also has been used to increase knee extension and improve hip flexion.[27] Although botulinum toxin is very effective in reducing spasticity, these improvements do not always lead to improved function. Reduction in spasticity may reveal underlying muscle weakness, which can lead to decreased stability for the patient and sometimes a greater likelihood of falling.[28]

Studies of upper limb spasticity have also demonstrated improvements with botulinum toxin treatment. In one study, children with hemiplegia, spastic diplegia, and spastic triplegia were assessed using the MAS, goniometer to measure range of joint motion, and Jebson Hand Function Test. Muscle power was also gauged. There was a statistically significant decrease in mean spasticity, range of joint motion, and hand function after injection. There was no statistically significant increase in muscle power, but parents did report improved function, including increased use of the hands and improvement in reaching, grasping, and releasing objects. Investigators noted that the temporary reduction in spasticity after injection with botulinum toxin creates the possibility for children to learn new functional skills.[29] Pain at the injection site seems to be the most common adverse effect but is not serious enough to preclude subsequent injections.

One of the largest studies of the use of botulinum toxin in children was a retrospective multicenter review of 758 children with spasticity (94% due to cerebral palsy).[30] Data were compiled from a total of 1,594 botulinum toxin type A (Dysport) injections. Adverse events occurred in 7% of total treatments, with focal muscle weakness reported most often. Analysis of the adverse event rate revealed that the incidence was related to the total dose administered rather than to the dose calculated by body weight. The highest incidence of adverse events was reported in patients who received more than 1,000 U of type A per treatment. Efficacy analysis revealed an overall response rate in 82% of patients, with treatment goals fully achieved in 3% of patients and partially achieved in 94% of patients. Younger patients achieved the best response, with effects diminishing with increasing age. Investigators concluded that botulinum toxin is safe and effective for the treatment of spasticity in children, but doses in excess of 1,000 U do not improve response and may increase the risk for adverse events.[30]

Dosing issues are of concern because there are no standardized guidelines for pediatric patients. In most studies, dosing of children is determined by body weight, muscle mass, and degree of spasticity. Chart review at three practice sites showed that doses of botulinum toxin type A for children with cerebral palsy have increased over time. The higher doses now used may reflect the greater number of injections administered to more muscle groups (in contrast to more conservative dosing in trials designed to assess more narrowly defined response in specific muscles). The same review also showed a trend toward younger children receiving higher doses of botulinum toxin type A, usually because they were too young or too small to be considered for more aggressive therapies, such as surgery and intrathecal baclofen. Older children had often undergone corrective surgery, and botulinum toxin was used as adjunctive therapy.[31]

The primary benefit of botulinum toxin therapy is the reduction in spasticity of agonist muscles, allowing improvement of weakened antagonist muscles and improved balance across the joint. Treatment is most effective in patients with dynamic muscle shortening localized to a few muscles and adequate selective motor control, and is less effective in generalized spasticity.[23] Good cognitive function is also associated with better outcomes because patients are able to follow instructions. Ideally, patients with spasticity due to cerebral palsy should be treated before age 5 or 6, or before the development of contractures.[23,28] For most patients with spasticity, regardless of cause, reduction in spasticity may improve results of complementary treatment with physical therapy and orthotics. This is particularly true with botulinum toxin treatment in younger children, in whom spastic muscles can still be stretched and the development of contractures can be delayed.[32] In some children with mild disease, there is evidence that early use of botulinum toxin may modify the natural history of cerebral palsy when it is used in combination with physical therapy and orthotics.[23,33]

Post-stroke spasticity

Patients who suffer stroke affecting the motor cortex may initially experience hypotonic muscle response, with spastic hypertonia following days, weeks, or even months later.[34,35] The effect on muscle function depends on the location and extent of stroke damage. Upper limb spasticity often includes adduction at the shoulder and flexion at the elbow and wrist. Lower limb spasticity may include hip and knee extension and ankle flexion.[35] Prolonged abnormal limb posture can lead to substantial deformity, affecting mobility, transfer, and hygiene, and contributing to pressure sores and pain. As with other approaches to the treatment of spasticity, post-stroke therapy should initially include a thorough assessment of beneficial spasticity (flexion) that may help in balance and mobility and negative spasticity that impedes function.

The reversibility of therapy with botulinum toxin may be especially useful in patients who have suffered stroke. In the weeks and months after stroke, some patients can regain function as they recover, especially when physical therapy is used. For patients who are achieving physical therapy goals, long-term antispasticity therapy is not always needed. Botulinum toxin therapy can be highly tailored to specific muscle groups, and doses can be adjusted according to muscle function.

Botulinum toxin has been evaluated in many studies of upper limb spasticity induced by stroke (Table 2).[36–41] Treatment with botulinum toxin has resulted in reduced spasticity, as measured by Ashworth and Modified Ashworth Scores, with few adverse effects noted. Fewer studies have been conducted in lower limb spasticity due to stroke, but early results show benefit in gait velocity among some patients receiving botulinum toxin injections into the plantar flexors.[42] Although studies consistently show reduced muscle tone following botulinum toxin therapy, these improvements do not always result in functional improvement. Investigators generally stress the importance of patient selection to achieve maximal benefit from therapy.

Long-term dosing effects of botulinum toxin have also been studied. This is of particular interest because of the extended recovery time needed for some stroke-induced injuries. A prospective study followed 28 patients with

TABLE 2. *Summary of studies evaluating botulinum toxin in upper limb spasticity from stroke*[36–41]

Study	Design	Treatment (total doses)	Outcomes
Bhakta 1996	Open-label pilot study 17 patients with nonfunctioning arm	400–1,000 U Dysport or 100–200 U Botox	Hand hygiene improved in 14/17 Putting arm through sleeve improved in 4/16 Walking improved in 1/4 Shoulder pain improved in 6/9 Wrist pain improved in 5/6 Passive ROM improved Benefit lasted 1 to 11 months No adverse effects
Simpson 1996	Randomized, double-blind, placebo-controlled, multicenter 39 patients with upper limb spasticity	75, 150, or 300 U Botox or placebo	300 U Botox resulted in statistically significant decrease in wrist flexor tone ($P = 0.026$) and clinically significant decrease in elbow flexor tone ($P = 0.199$) 6 weeks after injection No adverse effects
Sampaio 1997	Phase III open-label 19 patients with right or left spastic arm hemiparesis	150 U Botox	Median Ashworth score and joint mobility scores improved from 2 at baseline to 1 after 1 month of treatment Median FAT score improved from 0 at baseline to 1 after 1 month of treatment Function improvement rated as none or mild for 2/3 of patients
Bakheit 2000	Prospective, randomized, double-blind, placebo-controlled, dose-ranging 82 patients with MAS ≥2 for wrist, elbow, and finger flexors	500, 1,000, or 1,500 U Dysport or placebo	All 3 doses of Dysport produced statistically significant reduction in MAS in any joint at week 4 Reduction in elbow and wrist spasticity for all doses throughout the 16-week study period Reduction in finger spasticity for 1000 U dose throughout the 16-week period Adverse effects reported in 40.2%, but no serious effects were related to treatment
Bakheit 2001	Randomized, double-blind, placebo-controlled 58 patients	1,000 U Dysport or placebo	Reduction in total MAS score at week 4 ($P = 0.004$) Mean change from baseline in MAS at 16 weeks was −19.8 for wrist, −16.6 for finger, and −10.4 for elbow for the treatment group No serious adverse effects were related to treatment
Wang 2002	Open-label 16 patients with spastic hemiparesis	140 U Botox	Statistically significant improvement ($P < 0.05$) in muscle tone, joint ROM, hand muscle strength, and muscular pain lasted 8 to 12 weeks after treatment No functional improvement in 14/16 patients

ROM, range of motion; FAT, Frenchay arm test; MAS, modified Ashworth Scale; U, units.

upper limb spasticity after stroke who received botulinum toxin injections every 3 to 5 months for 2 years or longer. The observation period was 3 years. Objective measures were assessed using the MAS for spasticity, goniometry to measure range of motion, and the Frenchay Arm Test to evaluate function. Botulinum toxin type A (Botox) was injected using EMG. Total doses ranged from 50 to 300 U per patient. Botulinum toxin therapy resulted in improvements in technical outcomes and in activities of daily living. Motor dexterity improved for only eight of 28 patients. During the study, doses were not changed for any patient, but the intervals between injections lengthened. There was no change in effectiveness except for prolongation of benefit. Aside from transient pain at the injection site, there were no systemic or local adverse effects. Investigators concluded that the benefits of botulinum toxin continue even after long-term therapy.[43]

Another area of interest is whether therapy can positively affect the burden on caregivers. Spasticity leading to contractures can make it difficult to properly manage hygiene. In a unique placebo-controlled study of 40 patients with functionally useless arms due to spasticity, those receiving botulinum toxin type A (Dysport) had decreased disability, which translated into decreased burden for caregivers. Improvements in hand hygiene were particularly evident. Investigators concluded that the decision to use botulinum therapy should include consideration of caregiver burden.[35]

Trauma-induced spasticity

Patients who suffer brain or spinal cord injury from trauma often experience spasticity.[44] As with other populations, patients with trauma-induced spasticity achieve greater benefit if they are treated before contractures develop. The degree and location of damage from injury

dictates treatment approach, and localized injection with botulinum toxin provides advantages to patients who do not need systemic antispasticity treatment. As patients recover, botulinum toxin therapy can be tailored to very specific muscle areas.

Studies of the efficacy of botulinum toxin treatment have demonstrated improvements in spasticity even among patients with severe injury who have been unresponsive to other treatments.[45,46] In one study of six patients with severe brain injury, two were able to regain enough fine motor skills after treatment with botulinum toxin type A (Botox) to be able to write. Another regained enough hand function to assist with walking devices, and two others were able to dress and feed themselves after treatment. Long durations of response were observed.[45] These positive results support prior studies of traumatic brain injury in which the use of botulinum toxin produced increased range of motion, reduced severity of spasticity, increased extension of affected muscles, and decreased pain during physical therapy.[46]

BOTULINUM TOXIN FAILURE

Treatment failure with botulinum toxin has not been well studied among patients with spasticity. However, lack of therapeutic response has been observed in patients with cervical dystonia.[47] There are many potential reasons for treatment failure, including poor injection technique, injection at the wrong site, insufficient dose, unsuitable patient candidate for toxin therapy, and other issues related to administration of botulinum toxin. In addition, some patients simply do not respond to therapy either initially or during subsequent dosing after a successful initial response. Patients who fail to respond initially are classified as primary nonresponders and account for <1% of patients receiving therapy with botulinum toxin. The reason for this failure to respond is unknown. Patients who initially responded to treatment and then lose their response with subsequent injections are classified as secondary nonresponders. This decreasing response over time is believed to be due to the development of neutralizing antibodies and may occur in up to 10% of patients.[47] To minimize the risk for development of antibodies, it is recommended that patients initiated on botulinum toxin therapy be injected as infrequently as possible (no more than once every 3 months) and that the lowest effective dose be used. The serotypes of botulinum toxin (types A and B) are antigenically distinct, such that patients who develop resistance to type A can be effectively treated with type B, and vice versa.[48] If the patient develops resistance to one serotype, then use of an alternative serotype is recommended.

CONCLUSION

Botulinum toxin has been proved effective for the treatment of disorders associated with muscle hyperactivity. Although several effective treatment approaches are available for patients with spasticity, botulinum toxin provides a very effective means of targeting focal areas of spasticity. Patients with spasticity usually require several interventions in combination, such as physical therapy, oral antispasticity agents, and chemodenervation. For patients who may not be able to tolerate the adverse effects associated with oral medications, the use of botulinum toxin to address focal spasticity may allow decreased dosages of oral regimens. For patients who are especially susceptible to adverse effects, for example, children with cerebral palsy, botulinum toxin injections may afford fewer adverse effects and greater reversibility than phenol chemodenervation. Ease of administration via intramuscular injection with no need for anesthesia makes the use of botulinum toxin particularly attractive for pediatric patients.

Although existing studies show favorable effects of botulinum toxin in the treatment of spasticity, more data are needed, particularly to assess long-term results. Evaluating larger, more homogeneous populations using more rigorously designed studies is recommended to confirm and expand on the results that have been produced in smaller trials. In particular, more study is needed to better characterize the effects of botulinum toxin type B, the most recent addition to commercially available products. Until these data are reported, however, currently available information suggests that botulinum toxins will play an increasingly important role in the management of spasticity.

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