Spasticity is a centrally mediated, velocity-dependent increase in muscle tone that results in limitation of passive muscle stretch and overall limb movement. It is caused by interruption of descending inhibitory spinal motor pathways, with over-activity of alpha motor neurons. Disorders of the central nervous system, such as trauma, hemorrhage, infarction, infection, inflammation, space-occupying lesions or degenerative diseases, can lead to spasticity development. Other features of upper motor neuron (UMN) dysfunction, such as weakness, hyperreflexia and the development of contractures, usually accompany spasticity. For most patients, treatment of spasticity is essential for improving functionality, comfort and quality of life. For some patients, however—such as those in whom extensor tone of the lower extremities provides stability for walking, standing, and transferring—spasticity may actually be beneficial and need not be treated.

The approach to treatment should be multidisciplinary, including physical therapy (passive stretching and splinting), pharmacotherapy and surgery for severe contractures if needed. Over the years, numerous medications have been used successfully to treat spasticity. In this article, we provide an overview of these medications, including specific indications, dosing considerations, pharmacokinetics and side effects for each treatment modality. We also provide a practical, step-by-step approach for treating spasticity.

**Systemic Agents**

Baclofen (Kemstro), a structural analogue of γ-aminobutyric acid (GABA), is a pre- and post-synaptic GABA-B agonist that decreases alpha motor neuron activity. It may also reduce gamma motor neuron activity, thereby decreasing the sensitivity of muscle spindles involved in stretch reflexes. Baclofen is effective in reducing spasticity, decreasing paroxysmal painful spasms and improving range of motion, as shown in several trials of patients with multiple sclerosis and spinal cord disease. However, the use of baclofen for patients with spasticity of cerebral origin has little supportive data. This suggests that baclofen is more selective for spinal cord GABA receptors, and may be more useful in patients with spasticity of spinal origin.

Initial dosing is 5mg TID, with normal adult doses ranging between 20 to 80mg/day, given in divided doses TID or QID. In practice, doses of up to 120mg/day can be given cautiously for severe spasticity. Baclofen is rapidly absorbed after oral administration but CNS penetration is limited. Common side effects include muscle weakness, sedation and fatigue, and sometimes dizziness or nausea. It is partially metabolized in the liver and excreted by the kidney, and elevated liver function tests (LFTs) sometimes occur with patients receiving this medication. LFTs should be checked prior to treatment initiation and every six months thereafter. Memory impairment has been associated with baclofen administration in both humans and animals, and should be considered when initiating treatment in patients with poor cognitive reserve, such as those with...
stroke, traumatic brain injury and dementia. Baclofen withdrawal has been associated with seizures, hallucinations, hyperthermia and rigidity, so the medication should be tapered rather than abruptly discontinued.1,2,3

Tizanidine (Zanaflex) is a centrally-acting α2 receptor antagonist that inhibits the release of excitatory amino acids in spinal cord interneurons and may help promote the inhibitory action of glycine.1,2 It also inhibits type II sensory afferents1 that may affect the sensitivity of the muscle spindle. Tizanidine is effective in the treatment of spasticity due to MS, spinal cord injury and spasticity of cerebral origin.1,3 Initial dosing is 2-4mg TID, increasing every three days by 2-4mg/day up to 36mg/day in divided doses.1 Sedation, dry mouth and dizziness often limit its use. In one study of post-stroke spasticity, 89 percent of patients were unable to tolerate the maximum daily dose due to these adverse effects.7 We and many clinicians use a slower titration, especially in patients with cerebral disease.

Tizanidine is also metabolized by the liver and excreted by the kidney, so testing of LFTs should be performed prior to treatment initiation and every six months thereafter. Visual hallucinations have rarely been reported with doses above 24mg/day. Although no consistent effects on blood pressure have been found, concomitant use of antihypertensives, especially other medications with similar central α2-adrenergic activity (such as clonidine) should be avoided.3

Dantrolene sodium (Dantrium) inhibits muscle contraction by inhibiting the release of calcium from skeletal muscle sarcoplasmic reticulum, thereby interfering with excitation-contraction coupling necessary for muscle contraction. This effect is primarily on extrafusal fibers, but a minor effect on intrafusal fibers may alter muscle spindle activity as well.1,3 Placebo-controlled trials of dantrolene have demonstrated efficacy in decreasing spasticity, hyperreflexia, and clonus in spinal cord injury, cerebral palsy, MS and post-stroke patients.1,3 Initial dosing is 25mg daily for seven days, increasing by 25-50mg every four to five days to a maximum of 400mg/day.1,3 Zafonte et al. reported intravenous dantrolene therapy for severe spasticity in patients with traumatic brain injury, although this is not an approved application.

Given its direct action on skeletal muscle, the side effects of dantrolene are mostly peripheral; weakness is the most commonly reported side effect. Since weakness of unaffected muscles may limit its use, dantrolene may be best for those patients who are non-ambulatory with severe spasticity. Drowsiness, diarrhea and malaise are also reported. Rare cases of eosinophilic pleural and pericardial effusions secondary to dantrolene have been described.3 It is primarily metabolized in the liver and has been associated with hepatotoxicity, which is sometimes irreversible. Thus liver enzymes should be checked prior to initiation and every three months thereafter.1

Benzodiazepines bind to the GABA-A receptor, thereby increasing chloride conductance and resulting in presynaptic inhibition in the spinal cord. Diazepam (Valium) is the most frequently used benzodiazepine for the treatment of spasticity.1 Early trials of diazepam in spasticity found it to be more effective than placebo for patients with spinal cord injury, hemiplegia, and MS.1,3 Other studies have shown it to be comparable to baclofen.3,8,9 Initial dosing is 2mg BID, with titration to 60mg or more as needed to obtain a desired effect.1 As an alternative, a single nighttime dose of 5mg may be given if symptoms are primarily nocturnal or to avoid daytime sedation.1,3

Diazepam is well absorbed after oral administration and

This common sequela of many neurologic conditions severely reduces quality of life. Multimodal treatment can help alleviate spasticity and allow patients to improve motility.

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Picturing Freedom of Movement:
A Practical Approach to Alleviating Spasticity

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reaches peak concentrations after approximately one hour, with a half-life ranging between 20 and 80 hours. Diazepam can also be given intravenously, intramuscularly or rectally. CNS effects, such as sedation and cognitive impairment, can preclude attainment of doses adequate enough to effectively treat spasticity. Additionally, there is a risk of overdose, leading to coma and death, and a high potential for addiction and dependence. Rapid withdrawal of benzodiazipines has been associated with anxiety, dysphoria, psychosis, insomnia, intolerance for bright lights and loud noises, nausea, tachycardia, sweating, muscle twitching and sometimes seizures or death. Because it is metabolized in the liver, doses should be titrated carefully in those with hepatic dysfunction.

Clonidine (Catapres) is a centrally acting α2-adrenergic agonist that decreases sympathetic outflow and inhibits the release of glutamate. As an anti-spasticity agent, however, its primary mechanism of action is thought to be presynaptic inhibition of sensory afferents. Clonidine reduces the vibratory inhibition index in patients with spinal cord injury, and reduces muscle tone in patients with stroke, traumatic brain injury, intracerebral hematoma, and cerebral palsy. Clonidine has also been implicated in spinal neuronal recovery after chronic cord injury making it a good choice in those with spinal cord injury. Initial dosing is 0.1mg BID, with titration up to 0.3mg BID as tolerated. It is available in 0.1mg tablets or as a transdermal patch at 0.1mg or 0.2mg concentrations, designed to deliver the specified dose daily. Side effects, such as bradycardia, hypotension, dizziness, drowsiness, dry mouth, constipation, and depression often limit the utility of clonidine. Rapid withdrawal can result in a hypertensive crisis and should be avoided. In contrast to the reports of neuronal recovery in spinal cord patients, clonidine has been implicated in retardation of neuronal recovery after brain insult in both human and animals.

Gabapentin (Neurontin) binds to GABA receptors in the neocortex and hippocampus, effectively promoting the release of GABA. Recent studies have suggested some efficacy in treating functional impairments of spasticity associated with spinal cord injury or MS, but further studies are necessary to confirm these claims. Initial dosing is usually 300mg three times a day, increasing as tolerated up to a 3600mg maximum daily dose. We have used up to 4800mg/day for unrelated conditions without major adverse reactions. It is generally well tolerated, but somnolence, dizziness, and ataxia are common complaints with higher doses. It is well absorbed after oral administration, is not protein bound, is not metabolized by the liver, and is excreted unchanged in the urine.

The direct skeletal muscle relaxants, including carisoprodol (Soma), chlorzoxazone (Parafon Forte DSC), cyclobenzaprine (Flexeril), metaxalone (Skelaxin), methocarbamol (Robaxin) and orphenadrine (Norflex), have been approved by the Food and Drug Administration for the treatment of non-specific musculoskeletal disorders such as pain and cramping but are not approved specifically for spasticity nor have they been demonstrated effective for the treatment of this condition. The mechanism of action of these agents is not clear, but it is thought to be at least partially due to their sedative effects.

Although quinine has been reported to relieve muscle cramps and muscle spasms, there are no studies assessing its role in spasticity. Tetrahydrocannabinol, glycine, threonine, cyproheptadine, 4-aminopyridine, progabide and ivermectin have also been studied as potential antispasmodic agents, but the side effect profiles of some of these medications are limiting or data on these agents are inconclusive.

Botulinum Toxin

Botulinum toxin (BTX), which is the toxic product of the organism Clostridium botulinum, is a more novel agent used for the treatment of spasticity. BTX blocks the presynaptic release of acetylcholine from cholinergic nerve terminals, resulting in chemical denervation. Although at least seven immunologically distinct toxins have been isolated, local intramuscular injection of botulinum toxin type A (BTX-A) and type B are the only commercially available forms. BTX-A is marketed as Botox and Dysport and BTX-B as Myobloc/Neurobloc. After local injection, BTX spreads through muscle and fascia at a distance of approximately 30mm. Within 24 to 72 hours, there is focal extrafusal muscle paresis, with a maximal effect in five to 14 days. Given that BTX-A injections appear to reduce tone more than power, it is possible that there is also paresis of intrafusal fibers, with the diminished afferent input leading to decreased spindle sensitivity and reduction of spasticity. In 1989, BTX-A was approved by the FDA for use in strabismus, adult hemifacial spasm and blepharospasm. Since then, additional approved indications include cervical dystonia, primary axillary hyperhidrosis, and glabellar lines for cosmetics.

We have reported a double blind, placebo-controlled trial that demonstrated efficacy of BTX-A in reducing muscle tone in spastic elbow and wrist flexors in a dose-dependent fashion. Burbaud et al. found BTX-A effective for reducing muscle tone and spasms in hemiparetic patients with spastic feet. Additionally, there have been studies showing efficacy in CP and MS. While BTX has been approved for the treatment of childhood and adult spasticity in many European countries, it has not yet received FDA approval for these indications.

BTX may be most appropriate for those with residual power in the affected limb, and with movement impairment from antagonist overactivity. Electrophysiological guidance, with EMG or nerve stimulation, can help ensure a targeted treatment, and produces optimal results. Weakness is a possible side effect
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from BTX injection, especially if excessively dosed. Unintentional paresis of adjacent muscles may occur because of diffusion through muscle and fascia, and can be especially dangerous if affecting the pharyngeal or laryngeal muscles. Ultimately, this weakness is reversible. Other side effects of BTX include injection site reactions, or the development of antibodies to BTX, which may limit its efficacy. Should neutralizing antibodies develop to BTX, an alternate serotype may be used in follow-up treatment.

**Treatment for Refractory Spasticity**

When enteral medications fail and BTX treatments are not practical for a patient with severe, diffuse spasticity, intrathecal administration of baclofen should be considered. Only after a successful trial of a bolus injection of intrathecal baclofen should pump implantation be considered. With this treatment, baclofen is delivered directly into the CSF, allowing as much as four times the concentration of drug to be delivered at only one percent of the oral dosage. Since serum concentrations are lower, cerebral adverse effects are minimized.1

Several studies of intrathecal baclofen have shown dramatic results in patients with intractable spasticity of both cerebral and spinal origin, with improvement of muscle tone and spasms, pain and functional status.2-4 Infusion begins at 25µg/day, increasing up to an average of 400 to 500µg/day. Tolerance has been reported, and doses are often titrated up during the first six months to as high as 1500µg/day.1 Adverse effects, which occur mostly during dose titration, include sedation, headache, nausea, weakness and hypotension. Coma due to baclofen overdose has occurred, but is ultimately reversible. Surgery-related adverse events, including CSF leak, catheter dislodgment, spinal headache, meningitis, hematoma, incontinence, and wound infection occasionally occur.21 Mechanical pump problems or infected hardware are also risks.5

**An Approach to Treating Spasticity**

A reasonable initial approach to treating the patient with mild, diffuse spasticity is to start with an enteral agent. Although there are many systemic medications designed to treat musculoskeletal disorders, baclofen, tizanidine and dantrolene have the greatest wealth of supportive data, and are the only FDA-approved agents for the treatment of spasticity. Head-to-head trials of baclofen and tizanidine have shown similar efficacy and tolerability, but dantrolene has not demonstrated equal efficacy compared to the others.6

Hepatotoxicity is a concern with all three agents, so LFTs should be performed regularly. The best way to achieve clinical efficacy with the least amount of untoward side effects is to follow the adage “start low and go slow.” Diazepam is superior to placebo and is as effective as baclofen in the treatment of spasticity, but sedation and the potential for abuse, dependence and addiction limit its use. Therefore, diazepam is often used only as a supplement to one of the approved medications. Clonidine, although seldom used as monotherapy in the treatment of spasticity, is also a reasonable supplement to the approved medications, and may be of particular use in those with spinal cord injuries. The other enteral medications mentioned do not have enough supportive data and are best used as second-line treatment for spasticity.

For the treatment of focal spasticity, BTX should be considered early in the course of treatment. While head-to-head comparisons with oral agents are not yet available (the authors are conducting such a study), there are several advantages of focal injection therapy over oral medications. BTX treatment is localized and directed, especially when performed with EMG guidance, and provides improvement of muscle tone and painful spasms associated with UMN dysfunction without systemic side effects. In patients with intractable spasticity, refractory to other treatments, intrathecal baclofen administration may be considered. It is costly and requires skilled personnel for placement and monitoring. Thus, it should only be considered in those with severe functional disabilities that have not responded satisfactorily to other modalities. PN