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A Review of Spasticity Treatments: Pharmacological and Interventional Approaches

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Abstract

Spasticity is a velocity-dependent increase in muscle tone and uncontrolled, repetitive, involuntary contractions of skeletal muscles. Spasticity presents as upper motor neuron symptoms in patients with central nervous system pathology such as stroke, spinal cord injury, brain injury, or multiple sclerosis. As a result, a patient can have significant pain and limited mobility, which can lead to decreased quality of life and difficulty maintaining personal care. In this article we discuss mechanisms, indications, efficacy, and side effects of the most accepted current treatments. Currently available treatment options include oral medications and interventional procedures. Oral medications comprise centrally acting agents, such as baclofen, clonidine, and tizanidine, as well as anticonvulsants such as benzodiazepines and gabapentin and peripherally acting dantrolene. Interventional procedures include focal injections of botulinum toxin, phenol or alcohol, and an intrathecal baclofen pump. Surgical treatments include selective dorsal rhizotomy and neurectomy. We found that there are several treatments available with data to support their use, but many still need further research to prove their efficacy and develop optimal utilization.

Keywords

spasticity; treatment; upper motor neuron disease

I. Introduction

Spasticity is defined as a velocity-dependent increase in tonic stretch reflexes with exaggerated movements due to the hyperexcitability of stretch reflexes.¹ It is a well-known

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phenomenon seen in patients of all ages with a wide range of central neurological disorders.² It is often recognized as one component of upper motor neuron syndrome,³⁻⁵ the motor control changes that are seen after damage to an upper motor neuron controlling voluntary skeletal movement. Spasticity can be a feature of a single traumatic insult or from chronic neurological conditions.⁵ Some examples of upper motor neuron pathology include spinal cord injury (SCI), cerebral palsy, stroke, amyotrophic lateral sclerosis, and multiple sclerosis (MS). In fact, spasticity is the most commonly reported symptom for MS, seen in 90% of patients with the disorder.⁶ The changes seen in spasticity often manifest as increased tone, spasms, and/or clonus.³ Table 1 describes the characteristics and qualities of spasticity. Most cases of spasticity can be subdivided into spinal or cerebral spasticity.⁷ Spinal spasticity results from the removal or destruction of supraspinal control and leads to increased excitability of motor neurons, whereas cerebral spasticity stems from a loss of descending inhibition.⁸

Spasticity can be incapacitating. It can be triggered at any time through a variety of stimuli. External factors such as constipation, urinary tract infections, and pressure ulcers may exacerbate spasticity and its symptoms.^{3,9} Spasticity can also have functionally limiting and painful sequelae, including diminished joint mobility, decreased muscle flexibility, and sleep disorders secondary to airway obstruction.¹⁰ The location of spasticity depends on the lesion in the central nervous system (CNS). Often it presents in the lower back and legs,⁶ although upper body spasticity or pain is common, too. Left untreated, spasticity may lead to deformities, such as kyphoscoliosis and contractures, which can be difficult to correct.³ These deformities can cause significant difficulty in daily activities, especially maintaining hygiene and sexual relations.

While spasticity is very debilitating, it is amenable to drug therapies.⁴ The goal of treating spasticity is to palliate these symptoms to allow individuals to live with the least amount possible of discomfort and restriction without a significant number of side effects. This article discusses the variety of treatment options available and presents various opinions and options for the treatment of spasticity.

II. Treatments

Spasticity affects a patient's independence in activities of daily living such as hygiene, dressing, self-comfort, ambulation, and sleep.¹⁰ Later it may lead to significant pain, contractures, joint subluxations or dislocations, peripheral neuropathy, and pressure ulcers.¹¹ Therefore, treatment of this condition is imperative to improve quality of life and minimize medical complication. Spasticity can, conversely, be beneficial to help patients transfer, stand, ambulate, and maintain muscle bulk.

There are a variety of treatments available for controlling spasticity. Nonmedical treatments including physical therapies, occupational therapies, and complementary and alternative medicine are effective adjuncts to mainstream oral agents and interventional therapies. While each therapy has been shown to be efficacious in treating spasticity, the treatments themselves also come with their own adverse effects. In general, oral agents are more inexpensive in the short term and easier to use, but they have unwanted systemic effects,

which can outweigh the potential benefits they may provide.^{12,13} At the same time, these systemic drugs may be better for patients with generalized spasticity.⁵ On the other hand, interventional therapies pose the problem of procedural errors, difficulty in finding a provider who is trained to perform the procedure, and further complications.⁴ However, it may provide greater control of spasticity with fewer systemic side effects if patients are compliant and can tolerate the procedures. Because of the possible risks and benefits of each treatment, it is important to assess a patient's medical history to determine which treatment option is best.

A. Oral Agents

1. Centrally Acting Drugs

a. Baclofen: Baclofen is considered the first-line treatment for spasticity, especially in adult SCIs.⁵ It works pre- and postsynaptically as a gamma aminobutylic acid (GABA) B agonist at the spinal level¹⁴ and binds to its receptors, leading to membrane hyperpolarization. This restricts calcium influx, which subsequently (1) restricts endogenous excitatory neurotransmitters from being released and (2) inhibits mono- and polysynaptic spinal reflexes.^{2,4} Adverse effects include systemic muscle relaxation, sedation, and fatigue.¹⁴⁻¹⁶ Because of potential hepatotoxicity, there is a need to monitor liver function with baclofen use.¹⁷ Oral baclofen is not recommended for elderly patients because of excessive drowsiness.¹⁸ Furthermore, caution should be taken when treating patients in the recovery phase of brain injury because there has been some evidence of deleterious effects on brain plasticity.⁴ Withdrawing baclofen treatment has been associated with hyperthermia, seizures, and altered mental status,¹⁹ but these symptoms can be avoided by tapering off the drug gradually.

The oral form of baclofen is rapidly absorbed and crosses the blood-brain barrier.⁴ However, penetration of the blood-brain barrier is not very efficient, which explains the limited efficacy of oral baclofen in low doses (the efficacy of oral baclofen increases with higher doses). Studies using oral baclofen have reported significant improvement in flexion of the quadriceps in patients with MS when compared to a placebo (using the Ashworth scale²⁰) and subjective improvements in general function.^{21,22} Furthermore, one study showed the protective effects of oral baclofen on the deterioration in body musculature and metabolic profile that normally accompany spastic individuals with SCI.¹¹ While there is a breadth of studies demonstrating the effectiveness of baclofen, most studies adhere to testing the drug in the setting of a specific condition, such as MS or SCI.

b. Alpha-2 Agonists: Clonidine is an alpha-2 agonist that inhibits excessive afferent sensory transmission below the level of injury, decreasing spasticity.²³ In the past it was commonly used to diminish spasticity in patients with SCIs as well as to treat high blood pressure.²³ However, nowadays it is rarely used as a single agent in the treatment of spasticity because of adverse effects such as hypotension, bradycardia, and drowsiness.²⁴ Furthermore, some studies have shown that taking clonidine results in variable outcomes.²⁵ Thus, it may not be the most reliable option when treating spasticity.

Tizanidine often has been used in conjunction with other oral drugs, such as baclofen, for additive effects.¹⁶ It is an imidazoline alpha-2 agonist that decreases tone through an increase in the presynaptic inhibition of motor neurons. This action decreases the release of excitatory amino acids from spinal interneurons.⁴ Some studies have shown that tizanidine reduces spasticity from baseline on the Ashworth score compared to a placebo group and demonstrates a reduction in the frequency of daytime spasms.²⁶ Its half-life is short, so frequent dosing (usually every 6–8 hours) is required for it to be effective.⁵ However, the muscle weakness accompanying most oral antispastic drugs is less of a problem with tizanidine.²⁷ Common side effects are sedation, hypotension, xerostomia, muscle weakness, and hallucinations.^{2,4} Because of a potential side effect of modestly lowered blood pressure,^{14,28} tizanidine is contraindicated in patients taking hypertension medication.⁴ It also has been known to prolong the QT interval.¹⁷

c. Anticonvulsants

Benzodiazepines: Diazepam, a benzodiazepine, works postsynaptically on GABA_A receptors, depressing the action of the CNS. Along with clonazepam, another benzodiazepine, diazepam induces significant sedation.¹⁶ Because of this sedation, a potential benefit is the reduction of spasticity at night, permitting uninterrupted sleep. Diazepam has a tendency to act primarily on flexor reflexes,⁸ but it can work on extensors in higher doses. Because spinal spasticity has a propensity toward flexor reflexes, diazepam is better suited for spinal spasticity than for cerebral spasticity.⁸ However, these drugs also produce tolerance and dependence, limiting their long-term use.^{9,19}

Gabapentin: Gabapentin is usually given as an adjunct for spasticity treatments.²⁴ It has a structure similar to that of GABA but does not bind to those receptors.⁸ The exact mechanism of the drug is relatively unknown, but it is thought to act at the alpha-2_{δ1} subunit of voltage-dependent calcium channels, thus inhibiting calcium currents. Gabapentin is often prescribed when patients describe symptoms that are consistent with neuropathic pain along with spasticity.¹⁶ A study by Gruenthal et al.²⁹ showed that using gabapentin alone, compared to a placebo, demonstrated a reduction in the Ashworth scale and in the spasticity Likert scale scores. However, gabapentin is not a first-line treatment for spasticity and is rarely used as a monotherapy. Adverse effects include somnolence, tremor, and nystagmus.⁸

2. Peripherally Acting Drugs

a. Dantrolene Sodium: Dantrolene is the only oral antispasticity medication approved by the US Food and Drug Administration that works peripherally. It is often used in the field of anesthesiology to reverse malignant hyperthermia after delivery of anesthesia. As an antispastic drug it acts on the muscles themselves, uncoupling excitation and contraction by inhibiting calcium release at the sarcoplasmic reticulum.³⁰ Caution should be taken because there have been reports of liver failure with the use of the drug.^{14,30} Because dantrolene does not selectively target specific muscles, it may lead to the adverse effect of general muscle weakness.¹⁶ In some rare cases it has been fatal in high doses and is therefore not considered a first-line drug.⁹ However, it can be considered an adjunct in spasticity refractory to other treatments.²⁸

B. Interventional Treatments

1. Intrathecal Baclofen—The most common centrally acting intervention is the use of intrathecal baclofen (ITB), which uses the same mechanism of action as oral baclofen, but the medication is delivered in the CNS at the spinal level. Despite oral baclofen's ability to cross the blood-brain barrier due to its lipophilic nature, the efficacy is limited at lower doses and with severe spasticity.³¹ Thus a method was developed to supply baclofen intrathecally via an intrathecal catheter. This allows a higher CNS concentration of the drug at the spinal cord level at lower doses while avoiding the vast systemic side effects that oral baclofen induces. This intervention is most effective for lower limb spasticity because the drug concentration is believed to be highest at lower spinal level.⁹ A baclofen trial is recommended to confirm the efficacy of medication at the spinal level and observe the safety profile of the medication for the individual before permanent implantation of the an ITB pump.⁴ In addition to delivering a higher local concentration of the drug, one of the main advantages of this intervention is the ability to vary intrathecal infusion.⁴ Varying drug titration depending on the patient's activities allows more flexibility in self-care throughout the day, and it helps patients more effectively control nighttime spasms.^{2,32} The additional benefit of improving neurogenic bladder by decreasing bladder tone also has been reported.³³

The disadvantages of any mechanical implantable device are device failure and complications associated with device placement. Pump failure can lead to either overdose, resulting in respiratory depression and coma,³⁴ or withdrawal, resulting in hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation.^{35,36} Issues with the operative or perioperative management of the pump placement can lead to infection at the site of implantation and cerebrospinal fluid leak, leading to headaches.⁴ Arguments regarding the cost of this procedure as too high have been made; however, a recent cost-analysis showed favorable cost savings with long-term use.³⁷ Some studies have shown the effectiveness of ITB in reducing spasticity in MS and SCI.^{38,39} While the studies produced promising results, it should be noted that the sample size of participants with implantable devices is limited. Thus, more extensive studies are recommended to accurately demonstrate ITB's effectiveness.

2. Botulinum Toxin Injection—Botulinum toxin, commonly referred to as Botox (one of its trade names), is produced by the bacteria *Clostridium botulinum* and was originally used to treat strabismus.⁴⁰ It is currently the most widely used treatment for focal spasticity^{5,17} and avoids the generalized weakness and sedation accompanying oral medications.³ Botulinum works by inhibiting the release of vesicular acetylcholine from presynaptic nerve terminals at the neuromuscular junction.⁴¹ There are 2 different subtypes available, A and B, which differ in their level of purification and immunogenicity.⁴ Unlike other neurolytic drugs, the effects of Botox are reversible as the toxin begins to degrade, and effects last for 3–4 months.⁹ A thorough knowledge of muscle anatomy is required, and the use of electromyography to localize the targeted nerve is recommended.⁴ Botox has been shown to have better tolerance and efficacy than oral treatments⁴² and has been gaining widespread use, especially in patients with cerebral palsy.⁴³ A major side effect is possible dissemination to other areas of the body,⁴² which can lead to dysphagia if it is being used in

the upper limbs or neck muscles.⁴ The development of immunoresistance to the toxin can also be a potential problem.⁴² As with all injections, this procedure is to be used with caution in patients receiving anticoagulation therapy.

3. Phenol/Alcohol Injection—Phenol concentrations ranging from 3–7% or alcohol concentrations ranging from 50–100% are used to reduce spasticity by chemical neurolysis. These high concentrations are essentially injected perineurally to irreversibly destroy the nerve causing spasticity.^{4,5,17} This procedure is not commonly used as a first-line treatment because it is nonselective and has a variable duration of effect ranging from days to years⁸ because of partial nerve regeneration and sprouting following the treatment.^{4,5} This procedure is used mainly to help with gait, posture, and hygiene.⁴⁴ However, this is an effective treatment for patients with spasticity refractory to all other therapies^{5,16} and should be reserved for patients with a complete loss of sensation and/or no functional movement in their lower body.³ Caution must be taken because there can be potential adverse effects concerning the bladder, bowel, and sexual function.⁵ Other adverse effects include transient flushing⁴ and neuropathic pain.⁹ In current practice, this therapy is starting to be replaced by Botox injections.⁸

C. Spasticity in Children

Spasticity does unfortunately affect children, especially those with cerebral palsy and anoxic brain injuries, but treatment options are more restrictive compared to adults because of unfavorable side effects that are not tolerated well by children. A widely used therapy for children is botulinum neurotoxin injections. The American Academy of Neurology and the Practice Committee of the Child Neurology Society concluded that in localized spasticity, botulinum toxin A “should be offered as an effective and generally safe treatment.”⁴⁵ Side effects are the same seen for adults: fatigue, potential dysphagia, and pain at the injection site.³⁰ The risk of dissemination is still present, but health care professionals are urged to practice caution to avoid such an issue.³⁰ Botulinum toxin B has a tendency to cause more side effects, which is why botulinum toxin A is preferred.⁴⁶ However, it should be noted that while it is widely used, Botox is not yet approved by the Food and Drug Administration for the treatment of spasticity in children.⁴²

Selective dorsal rhizotomy (SDR) has been widely studied in children, especially in those with cerebral palsy, and can be very effective. Rhizotomy is a procedure that interrupts motor nerve signal transduction to reduce spasms and pain. It has shown significant reduction in spasticity in children, although the outcomes may be variable, and orthopedic complications, such as subluxation of the hips, may not be prevented.^{47,48} A study by Oki et al.⁴⁹ concluded that all the pediatric participants with spastic hemiparesis included in the study had a reduction of tone after SDR, as measured by a modified Ashworth scale, and showed an improvement in gait. Many adults who had SDR as children highly recommend the procedure as well.⁵⁰

Phenol injections have been used in the pediatric population but are poorly tolerated because of the adverse side effects of long-term pain and parasthesia.³⁰ One study showed that oral baclofen increased voluntary movement in children with cerebral palsy by initially reducing

spasticity.⁵¹ A weight-adapted dose of ITB has been used for children, but only if they are heavier than 15 kg.⁴ Some studies show that oral baclofen is well-tolerated in children.² However, it has been noted there are more complications seen in children using ITB than in adults.⁵² Furthermore, there are mixed results in studies assessing the effectiveness of baclofen in children with cerebral palsy.³⁰ Thus, further investigation regarding the efficacy of ITB for children is warranted.

D. Other Therapies

The potential use of cannabinoids for treating spasticity is a recent development, especially for patients with MS who are refractory to other therapies.⁶ Dronabinol and nabilone are 2 synthetic cannabinoids that have profound anti-nausea and anti-anxiety effects. Nabilone is the medication that was studied for spasticity control in patients with MS.⁶ The proposed mechanism of action is through the stimulation of the CB₁ receptors expressed in the output neurons of the substantia nigra pars reticulata and globus pallidus, thus suppressing excessive motor output and muscle spasms.⁵³ However, it has been shown that cannabinoids work both centrally and peripherally.⁵⁴ Evidence of the efficacy of this medication has been equivocal: One study showed that it may reduce symptoms of spasticity in patients with multiple sclerosis.⁵⁵ Another study states that cannabinoids for MS did not have a beneficial effect on spasticity in objective measurements, but there was support for a treatment effect on pain and spasticity in subjective measurements.⁵⁶ In theory, it may also reduce spasticity by reducing the input from noxious stimuli by reducing pain overall. Potential adverse effects are related to central nervous effects as well as the development of tolerance, thereby requiring extremely high doses.³⁰

Neurectomies (the removal of a peripheral nerve) are procedures that interrupt nerve signal transduction to reduce spasms and pain. Along with rhizotomies, today neurectomies are rarely performed⁹ in adults. Rhizotomies are used more for pain syndromes rather than spasticity, although relief of spasticity has been reported in some cases.⁵⁷ These interventional procedures may be considered if other treatment options do not provide sufficient control of spasticity.¹³

III. Discussion

Spasticity is described as a velocity-dependent increase in muscle tone and uncontrolled repetitive involuntary contractions of skeletal muscles.¹ Mechanisms of spinal spasticity include loss of supraspinal inhibition, loss of segmental inhibiting neurons, sprouting of collateral fibers, and changes in muscle fibers.⁵⁸ It is important to control this increased tone and muscle spasms to improve function during daily activities and self-care. Over time, spasticity can lead to contractures if it is not treated aggressively early in the course, which may lead to unnecessary complications and sequelae.

Oral antispastic agents are indicated when spasticity interferes with patients' activities of daily living or causes pain. However, as with any medication, high doses can produce unwanted side effects of the CNS without sufficient symptom control. Then interventional treatment options such as focal antispastic medication injections, intrathecal pump placement, or orthopedic surgeries can be considered. The goal is to relieve spasticity-

associated pain and limited function. A multidisciplinary approach with a combination of medication and physical therapy should help guide the treatment of spasticity. Even if medications are not sufficient, interventional therapies should be coupled with rehabilitation to reduce spastic tone, facilitate a return of functional motor control, facilitate functional independence, and improve quality of life in areas that pertain to the patient's deficits.⁵⁹

IV. Further Investigation

For ITB, there are currently 2 predominant philosophies of dosing: simple continuous infusion and flex dosing/periodic bolus infusion. Most patients with ITB pumps initiate their therapy with continuous infusion. Flex dosing is indicated when patients demonstrate a suboptimal response in spasticity control or the infusion rate reaches the daily dose of 200–300 µg^{59,60} without optimal control of spasticity. It is also thought that a bolus of ITB has a higher probability of reaching the upper spinal canal and upper extremities.⁶¹ A consensus panel for the use of ITB in stroke did not find a difference between simple continuous and flex dosing in terms of treatment goals.⁶² However, more studies with more rigorous inclusion criteria, a larger patient population, and different diagnoses are needed.

Another avenue of investigation for ITB is to determine the appropriate spinal level at which to place the catheter tip to optimize efficacy. The placement of the catheter tip for optimal management has not undergone rigorous clinical study. However, based on the favorable outcomes of Grabb et al.⁶³ and a study documenting the safety of cervical and upper thoracic placement,⁶⁴ recommendations for placement of the catheter tip can range from T2–T7 for upper extremity spasticity and T8–T10 for lower extremity spasticity. Further studies should be done to elaborate these findings.

There has not been much research investigating the effectiveness of combination therapy using multiple medications or interventional therapies in conjunction. Few studies showed that using electrical stimulation in conjunction with botulinum toxin A increased ankle flexibility and improved gait in children with cerebral palsy⁶⁵ as well as spastic foot drop after a stroke in adults.^{66,67} Another study alluded to the use of Botox as an adjunct to ITB to alleviate focal spasticity.⁶¹ However, research involving the treatment options discussed in this article is warranted for more definitive results.

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Abbreviations

CNS	central nervous system
GABA	gamma aminobutylic acid
ITB	intrathecal baclofen
MS	multiple sclerosis
SCI	spinal cord injury
SDR	selective dorsal rhizotomy

Table 1
Description of Characteristics and Qualities of Spasticity

Increased tone	An enhanced response to muscle stretch, as well as a decreased modulation of stretch reflexes ⁵
Spasms	Involuntary, repetitive, and sustained movements, usually involving multiple muscle groups and joints ³
Clonus	Involuntary contractions in a rhythmic pattern in response to sudden stretch of a muscle ³

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