Annals of Physical Medicine and Rehabilitation

Review Article

Spasticity Management: A Comprehensive Review of Pharmacological and Interventional Treatment

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Abstract

Spasticity, a common neurological disorder with diverse etiologies, poses a complex challenge for clinical management. Characterized as a velocity-dependent increase in muscle tone, it often leads to significant functional impairment and decreased quality of life. Addressing spasticity necessitates a multidisciplinary approach involving physical therapists, clinicians, and family support. Pharmacological treatments like baclofen, clonidine, tizanidine, benzodiazepines, gabapentin, and dantrolene offer relief, albeit with varying contraindications. Interventional treatments such as intrathecal baclofen, botulinum toxin injections, and surgical options like tendon lengthening or selective neurotomy provide targeted approaches, each with potential complications. While novel approaches such as cannabinoids and extracorporeal shock wave therapy present promising avenues but require further research. Successful spasticity management relies on a comprehensive understanding of underlying mechanisms, improved standardization of interventions, and ongoing interdisciplinary collaboration. This article serves as an updated review of spasticity management for the clinician.

Keywords: Pharmacological; Sclerosis; Cerebral palsy; Central nervous system

Introduction

Spasticity manifests as a pervasive neurological disorder with multifaceted etiologies, including stroke, multiple sclerosis, tumors, hypoxic brain damage, cerebral palsy, and traumatic brain injury. Traditionally and classically characterized, spasticity is a velocity-dependent increase in muscle tone, arising from an exaggeration of the stretch flex [1]. Central lesions disrupt the balance of supraspinal inhibitory and excitatory inputs directed to the spinal cord thus promoting the common clinical presentation of stiffness, muscle spasms, clonus, functional impairments, and pain [2]. Spasticity can be a complex disorder to manage therefore requiring a multi-team approach with the involvement of physical therapists, occupational therapists, clinicians, and careful family planning [3]. Effective management hinges on proper evaluation of spasticity, and a thorough understanding of the different approaches to take in treatment. The use of oral antispasmodic medications, such as baclofen, tizanidine, clonidine, benzodiazepines, and gabapentin has been useful in helping patients with a variety of disorders. In addressing focal spasticity-related issues, commonly employed interventions include injections of botulinum toxin, phenol, or alcohol. However, the transient nature of these effects in itself poses a limitation. Typically, as a final recourse, surgical options such as selective posterior rhizotomy, intrathecal baclofen pump implantation, and potentially deep brain stimulation may be considered [4,5]. In this review article, we will describe the various treatments and mechanisms behind spasticity management as well as discuss other therapy modalities.

Citation: Edogun E, Bandla M, Herman S. Spasticity Management: A Comprehensive Review of Pharmacological and Interventional Treatment. Ann Phys Med Rehabil. 2024; 2(1): 1011.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 11th, 2024

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Pharmacological Treatments

The goal of treatment in spasticity is to increase patient comfort and functional capacity. Keeping this in mind it is pivotal that patients are evaluated on the benefits of reducing symptoms of spasticity before treatment.

Baclofen

Oral Baclofen has been a cornerstone for the management of spasticity related to multiple sclerosis, spinal cord injuries, and other spinal cord pathologies since its US Food and Drug Administration (FDA) approval in 1977 [6]. It has shown to be an effective treatment for spasticity of both cerebral and spinal origin with oral baclofen being the most commonly used antispasmodic [7-9]. As a Gamma-Amino Butyric Acid (GABA) B receptor agonist, it functions by constraining calcium influx, thereby limiting the release of endogenous excitatory neurotransmitters. Moreover, it exerts inhibitory effects on both monosynaptic and polysynaptic excitation of motor neurons and interneurons within the spinal cord, helping to alleviate spasticity [10]. This culminates in reducing the action potential threshold in presynaptic type 1a neurons located on extrafusal muscle spindles. Simultaneously, there is a decrease in the amplitude of excitatory postsynaptic potentials originating from gamma motor neurons, which innervate muscle spindles [6]. Given that (GABA) B receptors are present on other neurons throughout the nervous system this accounts for the side effects typically seen in baclofen use. Most commonly showing as transient sedation, confusion, muscle weakness, and less commonly neuropsychiatric impairment hypotension, and in continence. The clinician must take extra caution with abrupt withdrawal of oral baclofen therapy due to the potential of causing seizures and hallucinations [11].

Clonidine

Clonidine is a centrally active alpha-2 adrenergic receptor-stimulating drug that has primarily been used for its antihypertensive properties but has been shown to decrease aspects of spasticity in patients with SCI [12]. This activation leads to a decrease in the release of excitatory neurotransmitters [13]. However, clonidine is rarely

used due to its various adverse effects such as severe bradycardia, drowsiness, constipation, depression, dizziness, and hypotension [14]. It is imperative to use gradual titration to mitigate adverse effects.

Tizanidine

Tizanidine is an imidazole derivative and similarly to clonidine works as a centrally acting alpha-2 adrenergic agonist, thus inhibiting the release of excitatory amino acids. It has been shown to reduce muscle tone and frequency of muscle spasms in patients with MS and spinal cord injury [15]. Clinical trials have demonstrated that the efficacy of tizanidine is comparable to baclofen or diazepam. Furthermore, more data is needed to evaluate the efficacy of tizanidine plus baclofen for improved spasticity control [16,17]. Common side effects are sedation, hypotension, muscle weakness, and hallucinations. It has also has been shown to prolong QT interval as well [17].

Benzodiazepines

Benzodiazepines, exemplified by diazepam, exert their action postsynaptically on GABA A receptors, inducing Central Nervous System (CNS) depression. As one of the earliest antispasticity medications, diazepam demonstrates efficacy on par with baclofen [18]. Noteworthy side effects encompass sedation and modulation of memory and attention. The potential for physical dependence underscores the importance of a gradual tapering approach when discontinuing benzodiazepines, given concerns regarding withdrawal [19]. Withdrawal symptoms may manifest as agitation, irritability, tremors, nausea, seizures, and insomnia, necessitating careful and judicious management.

Gabapentin

Gabapentin, developed to emulate Gamma-Amino Butyric Acid (GABA), does not engage with GABA receptors. While the precise mechanism of action remains incompletely elucidated, current evidence suggests a focus on α2δ-1, an auxiliary subunit of voltage-gated calcium channels [20,21]. This inhibits the release of excitatory neurotransmitters in the presynaptic area. A double-blind placebo-controlled crossover study showed that gabapentin was associated with significant improvements in patient ratings of spasticity and Ashworth scale score [20]. Noting that gabapentin can have substantial usefulness in patients with spasticity and neuropathic-related pain [20]. While gabapentin has been employed off-label for spasticity treatment, there is a need for future studies to systematically investigate the comparative efficacy of the combination of gabapentin and baclofen *vs.* baclofen monotherapy in the management of spasticity.

Dantrolene

Dantrolene, a peripherally acting skeletal muscle relaxant used to play a crucial role in managing spasticity with a variety of etiologies. Derived from hydantoin, this drug acts by interfering with the release of calcium ions from the sarcoplasmic reticulum in muscle cells, thereby preventing excessive muscle contraction [22]. Clinical trials from the 1970s demonstrated that dantrolene is superior to placebo in adults or children with spasticity from various causes [23], nonspecific targeting of muscles by dantrolene may result in generalized muscle weakness, drowsiness or dizziness, and a sense of overall malaise. Prolonged dantrolene therapy has been linked to hepatic toxicity, potentially posing challenges for individuals undergoing treatment for muscle spasticity disorders [22]. With the introduction of several oral medications employed after dantrolene, it has become a less utilized treatment modality for many clinicians [24].

Interventional Treatments

Intrathecal baclofen

Intrathecal baclofen is a highly productive intervention for the management of severe spasticity. Intrathecal administration allows for direct delivery of baclofen into the CNS via an intrathecal catheter [25]. Although oral baclofen is effective it is limited by needing high doses and garnishes a half-life of 5-6 hours. A continuous intrathecal baclofen pump allows for smaller doses and avoids many of the widespread side effects of oral baclofen therapy, such as sedation, excessive weakness, and mental confusion. It has shown effectiveness in improving functional outcomes with significant decreases in mean Ashworth scores in patients with spasticity of various etiologies [26,27].

Concerns with using intrathecal baclofen pumps are similar to most implantable devices. Technique differences in implantation can lead to infection or damage to the device [28]. Pump failure can manifest as baclofen overdose or baclofen withdrawal. Clinicians must have a high diagnostic index of suspicion for the nature and severity of toxicity symptoms. Symptoms can range from mild symptoms such as confusion, lethargy, and somnolence to life-threatening hemodynamic instability, seizures, cardiac arrhythmias, and respiratory failure [29].

Withdrawal symptoms from oral baclofen can occur when there is an abrupt discontinuation or a decrease in dosage. The risk of severe withdrawal symptoms significantly rises with sudden cessation due to human error, malfunction of the Intrathecal Pump (ITP), or migration of the intrathecal catheter [29]. These symptoms often present as Altered Mental Status (AMS), aggravated spasticity, fever, nausea, weakness, and autonomic instability. In more severe cases, symptoms may escalate to include rhabdomyolysis, profound autonomic instability, cardiac arrest, and, in extreme cases, death [30,31]. Therefore, cautious titration of doses in Intrathecal Baclofen (ITB) drug administration is crucial. The key to managing baclofen withdrawal is the prompt re-initiation of baclofen dosing [6,32]. Providing an Intensive Care Unit (ICU) level of care and ensuring continuous hydration with Intravenous (IV) fluids is vital to prevent rhabdomyolysis and ensure proper management [33].

Botulinum injections

Botulinum toxin is a potent neurotoxin derived from the Clostridium botulinum bacteria. It exerts its effect by binding to presynaptic cholinergic-nerve terminals and decreasing the release of acetylcholine at the neuromuscular junction. There is paralysis and decline of miniature end-plate potential within a few hours of injection of botulinum toxin [34]. There are a variety of botulinum toxin variations but the most common are the neurotoxin type a preparation [35]. The three leading botulinum neurotoxin type A products on the market in the western hemisphere are on a Botulinum toxin (ONA; Botox), a Bobotulinum toxin A (ABO; Dysport) and in cobotulinum toxin A (INCO; Xeomin) [35] Botox, comprises 85 percent of the worldwide Botulinum toxin market. Other formulations include a bobotulinumtoxinA (Dysport®) which differs from Botox mainly by its purification process and dose ratios. Clinical and preclinical data suggest that a conversion ratio between Dysport and Botox of 3:1 or even lower could be appropriate for treating spasticity [36]. IncobotulinumtoxinA (Xeomin®) is considered to be deemed a purer formulation of botulinum toxin type A due to decreased amounts of complexing proteins and is used with a 1:1 conversion ratio with

Botox. It is imperative to note that although all three have similar efficacy when properly dosed, Dysport has been shown to have a better cost-efficacy profile [35,36]. While exact dosing and injection sites are tailored to individual patients and specific muscles involved in spasticity, the effects of the toxin typically last ~3 months due to its degradable nature [37]. Adverse effects associated with botulinum toxin injection are few but providers should be cautious in identifying signs of local and hematogenous spread to unintended areas. This can manifest as dry mouth, flu-like mild malaise, and headaches [38].

There is considerable evidence that BTX injection into spastic muscles reduces the resistance of passive movement in joints and improves resting posture [37-40]. However, the ability to demonstrate improvement in the active function of paretic limbs has been a difficult challenge for clinical research. When evaluating botulinum toxin used for lower limb spasticity, outcome measures have mostly been variable and minuscule [41,42]. Although a recent small single-center study has demonstrated improvement in gait and postural control in patients with post-stroke spasticity [43].

Tendon lengthening

There is a myriad of surgical approaches that have been used when dealing with spasticity management. Tendon lengthening is an orthopedic intervention that involves surgical elongation of tendons to affect the force-generating capacity of muscles and improve joint range of motion [44]. It ultimately functions to rebalance muscle forces and alleviate spasticity-related deformities, most likely due to an alteration of the Golgi receptors and muscle spindles in the muscle. Although it is considered to be a safe and effective method, success depends on careful patient selection. As tendon lengthening may lead to over lengthening of the tendon and weakness [45].

Dorsal longitudinal T-myelotomy

Dorsal longitudinal T-myelotomy is an antiquated surgical procedure involving the creation of an incision in the spinal cord to selectively interrupt specific nerve pathways. Initially established as an effective approach for treating severe spastic paraplegia, the intervention aims to reduce excessive muscle contractions and alleviate spastic symptoms by disrupting aberrant neural signaling. A comprehensive 1991 review, encompassing 20 cases of longitudinal myelotomy, revealed that 17 patients experienced marked reduction or complete cessation of antispasmodic medications [46]. However, with chronic intrathecal baclofen infusions, this once-utilized procedure has fallen out of favor, marking a shift in clinical preference towards more contemporary and targeted spasticity management approaches [46]. Recent studies have reported consistent findings with this relatively uncommon neurological procedure, demonstrating statistically significant postoperative enhancements in both spasticity and passive range of motion [47] while the limited frequency of the procedure in previous studies poses a constraint; there is optimistic potential for its role in addressing refractory spasticity. The authors also suggested its applicability in regions where an intrathecal form of baclofen is unavailable or among patients facing financial constraints, programmable pump devices inaccessible [47,48]. These findings collectively underscore the possibility of further utilization of dorsal longitudinal myelotomy for severe spasticity management.

Selective neurotomy

Selective neurotomy involves surgical cutting of peripheral nerves and serves as a potential permanent option in spasticity management. For instance, in selective tibial neurotomy, there is a microsurgical dissection of each tibial nerve branch at the lower part of the popliteal region to treat spastic equinavarus foot [49]. This approach like many neurotomy procedures should only be considered after proper trial of physical therapy and pharmacological. 49 Although typically seen as a last resort there is strong evidence of long-lasting benefit with the use of selective neurotomy [50]. Selective Dorsal Rhizotomy (SDR), on the other hand, operates by selectively targeting dorsal nerve roots in the spinal cord. This procedure is frequently employed for treating lower limb spasticity in children with cerebral palsy, and it is underpinned by robust medical evidence supporting its efficacy [51].

In adults, the utilization of Selective Dorsal Rhizotomy (SDR) continues to yield significant improvements; however, it appears to be associated with more negative outcomes compared to childhood interventions. According to one survey, 50% of participants reported varying levels of postoperative numbness in the legs [52]. The cause of this phenomenon is unclear, but one can consider the increased functional decline associated with persistent Cerebral Palsy (CP) as a potential contributing factor. As with any interventional approach, it is imperative to carefully assess and weigh the potential side effects of Selective Dorsal Rhizotomy (SDR) on the progression of spasticity.

Phenol and alcohol injections

The administration of alcohol or phenol results in protein denaturation and neurolysis which can allow passive limb mobilization to prevent fixed soft tissue contractures [53]. Phenol nerve in filtration provides a temporary motor nerve block that lasts for weeks or months [54]. Phenol must be used at a concentration above 3% as it denatures proteins and injures cells more effectively at this concentration. Phenol and alcohol are both easily available options for the clinician and would be very beneficial for resource-limited areas. Due to the effectiveness of botox injections, phenol/alcohol has run out of favor. Studies have shown that after injection of phenol, a significant decrease in muscle tone was only observed for 6 weeks whereas injections of BTX-A lasted for up to 12 weeks in patients with Cerebral palsy [55]. Although chemical neurolysis with phenol is considered to be a relatively safe and cost-effective method to reduce spasticity it still has several clinical disadvantages including skin irritation, permanent peripheral nerve palsy, and painful muscle necrosis [55,56].

Cannabinoids

The use of cannabis in spasticity management has garnered increasing attention and exploration over the years [57]. The primary active compound, (−)-trans-Δ9-tetrahydrocannabinol or THC, is believed to exert its effects by binding to CB1 and CB2 receptors. It is thought that CB1 receptors are present in high concentrations in the central nervous system [58]. A substantial body of evidence regarding the impact of cannabinoids on spasticity has emerged predominantly from studies conducted in individuals with multiple sclerosis. Seven out of eight crossover studies demonstrated positive outcomes, revealing that synthetic cannabinoid such as dronabinol and nabilone, cannabis extracts, and smoked cannabis exhibit improvements in various measures of spasticity. It is crucial to highlight, however, that numerous studies did not identify a significant effect of cannabinoids on spasticity when assessed using the Ashworth scale. This suggests a nuanced relationship between cannabinoids and spasticity, emphasizing the need for further exploration and understanding of specific mechanisms and contextual factors influencing their efficacy in diverse patient populations [59].

Extracorporeal shock wave therapy

Extracorporeal Shock Wave Therapy (ESWT) presents an intriguing prospect for patients with spasticity, providing a safer treatment modality that circumvents the need for injections or pharmacotherapies. These shock waves are characterized by a sequence of individual sonic pulses, distinguished by high peak pressure, rapid pressure rise, and short duration [60]. Ongoing researches are dedicated to discerning the precise mechanism through which these shock waves influence the neuromuscular junction. Some studies have explored the notion that the application of shock waves induces the degeneration of acetylcholine receptors [61]. Researchers have posited that ESWT may augment intracellular Nitric Oxide (NO) production, leading to additional anti-inflammatory effects. This prompts consideration of whether such mechanisms could play a role in addressing spasticity [62]. Nonetheless Data from the 90s had shown the potential for extracorporeal shock wave in treatment of muscle dysfunction and hypertonia [63]. The idea that a single, active treatment of shock wave therapy on spastic muscles can lead to a significant reduction in muscle tone provides a safe and noninvasive method to help patients with spasticity. Many physicians have begun to use ESW therapy in their clinical practice but its use has not been fully gained acceptance as a plausible treatment modality. This may be because its mechanism is not fully understood, there is no standardization of treatment, and significant randomized clinical trials testing its efficacy will not yet be standardized [64]. Although it poses as an exciting tool for the treatment of spasticity.

Discussion

Spasticity, a neurological disorder stemming from various etiologies such as stroke, multiple sclerosis, and traumatic brain injury, presents a complex challenge in its management [1]. The traditional characterization of spasticity involves a velocity-dependent increase in muscle tone, resulting in stiffness, spasms, and functional impairments. If not treated early in its clinical course, spasticity can lead to contractures, pain, and permanent joint deformity. Addressing this multifaceted condition requires a comprehensive, multi-team approach involving physical therapists, occupational therapists, clinicians, and family planning [3].

In the realm of pharmacological treatments, various medications have shown efficacy in managing spasticity [1]. Baclofen, a GABA B receptor agonist, effectively reduces spasticity by limiting the release of excitatory neurotransmitters. Clonidine and tizanidine, as centrally acting alpha-2 adrenergic agonists, also demonstrate benefits, though adverse effects necessitate cautious use. Benzodiazepines, gabapentin, and dantrolene offer alternative pharmacological avenues, each with distinct mechanisms of action and associated side effects. While these medications provide relief, the transient nature of their effects underscores the need for ongoing research and innovative approaches. Interventional treatments, such as intrathecal baclofen, botulinum toxin injections, and surgical options like tendon lengthening or dorsal longitudinal T-myelotomy, offer more targeted approaches. However, each comes with its set of challenges and severe potential complications. Selective neurotomy and cannabinoids present novel avenues, but careful consideration of risks and benefits is paramount. The use of extracorporeal shock wave therapy introduces a noninvasive and potentially safer alternative, although its mechanisms and standardization require further exploration [64], while the promising prospect of cannabinoids in spasticity management highlights the need for a nuanced understanding of their effects and potential applications [59].

In conclusion, the management of spasticity has the potential for continued improvement, with a plethora of treatment modalities available. Future advancements hinge on a deeper understanding of the underlying mechanisms, improved standardization of interventions, and ongoing research to explore novel approaches. A holistic and individualized approach, involving collaboration across healthcare disciplines, remains crucial in addressing the diverse and challenging landscape of spasticity management.

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