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## Review & Analysis

# Antispasticity Medications Uses and Limitations of Enteral Therapy

**ABSTRACT**

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**Key Words:** Spasticity, Antispasticity Medications, Enteral Therapy

**S**pasticity can be the result of numerous conditions and remains a vexing problem for clinicians and patients. Although several medications have been approved for utilization in persons with spasticity, the literature has yielded no clear standard of care. The purpose of this review is to describe presently available medications and to discuss some options for the future. At present, medications are chosen by physicians based on a limited data set and an appreciation of the potential side-effect profile for those being treated. A clear concern with such agents has been improvement in clinical measures of spasticity with only limited carryover to improved function. In this review, we have divided the discussion in terms of historical perspective (i.e., those agents that have traditionally been used to treat spasticity and those that represent newer medications or novel concepts). This review will focus on enteral medications only and will not review either neurolytic or intrathecal therapy.

**Traditional Medications**

**Dantrolene Sodium.** Dantrolene is used in patients with muscle spasticity and is the only known effective treatment for malignant hyperthermia. Ward et al.<sup>1</sup> stated that dantrolene sodium acts primarily by affecting calcium flux. However, its effects on muscle relaxation and energetics are unknown and may have important consequences in diaphragmatic function.<sup>2</sup> Dantrolene sodium is 1([5-(nitrophenyl)furfurylidend] amino) hydantoin sodium hydrate. It is indicated for use in chronic disorders characterized by skeletal muscle spasticity, such as spinal cord injury, stroke, cerebral palsy, and multiple sclerosis. Dantrolene has specific action at the sarcoplasmic reticulum by inhibiting calcium activity. Dantrolene is believed to act directly on the contractile mechanism of skeletal muscle to decrease the force of contraction in the

absence of any demonstrated effects on neural pathways, on the neuromuscular junction, or on the excitable properties of the muscle fiber membranes.<sup>3</sup> This may be a theoretical advantage over other agents that manifest their efficacy through the central GABA pathways with the associated potential interference with neural recovery. Dantrolene has been evaluated in the treatment of those with cerebral palsy, multiple sclerosis, and spinal cord injury. Wuis et al.<sup>4</sup> described the kinetics of dantrolene metabolism and noted that hydroxylation is primarily responsible for excretion of the dantrolene molecule from the body.

Laboratory evaluation of the potential role of dantrolene in the management of spasticity raises some compelling issues. Nakayama et al.<sup>5</sup> noted that intracerebroventricular dantrolene prevents delayed neuronal loss in the rat hippocampal CA1 region of rats subjected to transient ischemia. Popescue et al.<sup>6</sup> has demonstrated that dantrolene sodium may protect against kainic acid-induced apoptosis. Although this evidence is quite preliminary, there may be some theoretical advantages of dantrolene sodium in the acute care setting.

Steinberg et al.<sup>7</sup> studied the effects of dantrolene sodium on 23 patients with hemiplegic spasticity of various pathogeneses. The drug was most effective in reducing or abolishing clonus and somewhat less efficacious in decreasing the resistance to stretch and the tendon reflexes. These authors reported that gait was improved and that the patients found it easier to take care of their personal needs. In general, motor performance was improved. Of interest is a study of enteral administration by Meyler et al.<sup>8</sup> in which 25 patients with spasticity underwent evaluation for the pharmacokinetics and effects of dantrolene sodium after prolonged administration. The results were better with 100 mg daily than with a

higher daily dose. An increase of the daily dose from 200 to 400 mg was not associated with higher blood levels. Katrak et al.<sup>9</sup> evaluated 31 patients in a double-blind, placebo-controlled trial. A modified Cybex isokinetic dynamometer was used to gather information on strength and muscle tone. Dantrolene was noted to reduce strength in the unaffected limb but did not alter strength in the paretic limb. In addition, dantrolene produced no change in functional outcome or biochemical tests at doses of 200 mg/day. In another study, 19 patients with spastic paresis receiving dantrolene therapy were studied in an attempt to better understand the specific pattern of Dantrium action.<sup>10</sup> Clonus was abolished in 14 of 15 patients with this sign. The responses to local cooling were used to differentiate alpha and gamma spasticity. Reduced passive resistance was observed in 16 muscles with alpha spasticity and four of the muscle groups showing gamma spasticity.<sup>10</sup> Joynt<sup>11</sup> noted that dantrolene sodium was effective at reducing muscle spasms, and Achilles tendon tap but functional improvement was rare.

Dantrolene was compared with diazepam in a two-part, double-blind study of 22 children with spasticity.<sup>12</sup> The combination of both drugs seemed to be the most effective. Haslam and Walcher<sup>13</sup> found an improvement in deep tendon reflexes and scissoring among children with cerebral palsy. A recent review noted that dantrolene has been found to be efficacious in cerebral palsy-induced spasticity and compares favorably with baclofen and diazepam.<sup>14</sup> Among those with spinal origin spasticity, dantrolene may have limited utility. Few studies exist to support the use of this medication in the spinal population, and dantrolene's propensity to cause peripheral weakness limits its utility. In the 1970s, Glass and Hannah<sup>15</sup> compared dantrolene with diazepam among a population

with spinal origin spasticity. They noted important improvements in spasticity, but treatment with dantrolene was limited by weakness. The authors of this article often employ it in the treatment of those with spasticity of cerebral origin. Ketel and Kolb<sup>16</sup> noted a significant decline among chronic stroke patients who had dantrolene discontinued, suggesting a potential benefit. Chyatte et al.<sup>17</sup> evaluated nine stroke patients treated with dantrolene and noted improved range of motion; however, function was not positively affected.

Doses begin at 25–50 mg and increase by 25–50 mg every 4–5 days to a maximum of 400 mg/day. Among children, the dosage has been as high as 12 mg/kg/day. Dantrolene has the advantage of minimal cognitive side effects and only modest interactions. The authors have occasionally employed the use of intravenous dantrolene therapy for severe spasticity in persons with traumatic brain injury; however, this should be done with great caution. Dantrolene therapy has been associated with hepatic toxicity.<sup>18</sup> This is especially true when other agents that may facilitate hepatotoxicity are in use, and careful monitoring of liver function profiles are warranted. Durham et al.<sup>18</sup> has reported that the hepatotoxicity is not related to biotransformation issues, whereas Chan<sup>19</sup> has discussed that those at highest risk are women of >40 yrs of age and those receiving >300 mg of dantrolene. Dantrolene inhibits platelet activation mainly due to suppression of phosphoinositide breakdown.<sup>20</sup> This could be a concern in the post-multiple trauma patient in whom bleeding is an issue. Nogen<sup>21</sup> completed a phase 2 study of 21 pediatric patients and concluded that dantrolene sodium does not adversely affect the frequency of seizures in children with known epilepsy and spasticity. Felz and Haviland-Foley<sup>22</sup> have reported that dantrolene has been associated with an eosinophilic pleural effusion syn-

drome. Although Dohen et al.<sup>23</sup> noted six cases of pleurisy induced from its use, in all six cases, the pleurisy was observed with a peripheral eosinophilia and occurred after >60 days of therapy. Pericardial effusions occurring in association with pleural effusions or independently have been reported in association with dantrolene treatment.<sup>24</sup> Pembroke et al.<sup>25</sup> have reported two cases of severe acneiform eruption induced by dantrolene sodium, with both cases occurring in middle-aged women.

**Baclofen.** Baclofen is active at the GABA<sub>B</sub> receptor both presynaptically and postsynaptically. It has been employed for the treatment of spasticity in persons with spinal cord injury, cerebral palsy, multiple sclerosis, stroke, and brain injury. The majority of studies demonstrating the efficacy of baclofen have been in persons with spinal cord injury and multiple sclerosis.<sup>26</sup> Although data have shown some improvement in flexor spasms and measures of spasticity, functional carryover has been less than impressive. Studies by Basmajian and Yucel<sup>27</sup> and Pederson et al.<sup>28</sup> have demonstrated a failure to improve functional ambulation or activities of daily living. Nielsen et al.<sup>29</sup> and Nielsen and Sinkjaer<sup>30</sup> provided a potential explanation for this issue by demonstrating that baclofen reduced ankle stiffness and increased ankle response latency; however, this was offset by a decrease in soleus strength.

Baclofen seems effective at improving flexor spasms among those with spinal cord dysfunction; however, little data exist to show improved activities of daily living or ambulatory capacity. A Scandinavian study of 14 persons with multiple sclerosis noted no significant functional improvement among those treated with baclofen.<sup>31</sup> For those with spasticity of cerebral origin, little efficacy has been demonstrated. In a review of traditional spasticity med-

ications, Gracies et al.<sup>32</sup> noted that the use of baclofen in the treatment of cerebral origin spasticity has little support. Such therapy is often limited by the side-effect profile and by questions regarding efficacy. Several years ago, a single study of baclofen therapy for children with cerebral palsy demonstrated improved range of motion and spasticity while showing a reasonable tolerance profile.<sup>33</sup> This agent seems most effective for those with spasticity of spinal pathogenesis. Enteral baclofen therapy may be warranted for those with severe spasticity of cerebral origin who cannot tolerate dantrolene sodium and face the risk of severe contracture or loss of range of motion.

Baclofen has been noted to produce sedation, especially among those with cerebral disorders. Concerns with the use of this medication include asthenia, depression, hallucinations, nausea, dizziness, and paresthesias.<sup>3</sup> Attention and memory deficits have been raised in animal models and observed with humans. GABA<sub>A</sub> facilitatory agents may impair recovery.<sup>34</sup> Wallace et al.<sup>35</sup> reported that agents that act postsynaptically at the GABA receptor can be associated with impaired functional recovery in an animal model. The phenomenon has not been evaluated in a model utilizing intrathecal delivery systems. Memory dysfunction has been associated with baclofen therapy in both animals and humans.<sup>36,37</sup> Additional concerns with baclofen include lowered seizure threshold and withdrawal syndrome.<sup>38</sup> Rapid withdrawal from baclofen therapy should be avoided and can induce seizures, altered mental status, hallucinations, hyperthermia, and rigidity.<sup>39</sup>

**Cyproheptadine.** Cyproheptadine is an older agent developed for treatment of allergic symptoms. It has been employed to help increase caloric intake in those who are undernourished and those with insufficient weight gain.<sup>40</sup> The medication seems

to act at a number of transmitter sites, including serotonin, histamine, and acetylcholine.<sup>41</sup> Perhaps its most profound effect is on the serotonin system, and it has been used to treat serotonin syndrome.<sup>42</sup> Cyproheptadine has been shown to improve gait in those with clonus,<sup>43</sup> with Barbeau et al.<sup>44</sup> reporting that cyproheptadine seems to decrease clonus in a population with spasticity of various spinal origins. When prescribed, this agent should be given at night secondary to the risk of sedation, and patients must be carefully monitored for this potential problem. This side effect may limit the utility of cyproheptadine in those with cerebral origin spasticity. Dosage is usually started as 4 mg at night and increased every 5 days to a maximum of 16 mg. Of interest, cyproheptadine has been used to treat baclofen withdrawal symptoms.<sup>45</sup>

**Benzodiazepines.** Benzodiazepines are the oldest family of medications used for spasticity. Diazepam, the most commonly used agent, acts near the GABA<sub>A</sub> receptor to hyperpolarize the cellular membrane, and thus increases presynaptic inhibition<sup>46</sup> of polysynaptic and monosynaptic reflexes. These agents may be administered enterally or via intravenous administration. Benzodiazepines demonstrate their action by potentiating the GABA system. This is the same system that baclofen activity is mediated through, and therefore, concerns are raised regarding a potential negative effect on neurorecovery.<sup>47</sup> Early studies of the use of diazepam in spinal cord injury, cerebral palsy, and multiple sclerosis demonstrated its efficacy in the treatment of spasticity over placebo.<sup>47-51</sup> Diazepam's major limitation is in its rather significant side effect profile. In head-to-head comparisons with other agents, sedation limited tolerance of diazepam.<sup>48-52</sup> Because of this potential, it is rarely recommended as a first- or second-line agent in persons with

brain injury or stroke. The sedation effect can be amplified with the use of alcohol. Diazepam overdose can lead to somnolence, coma, or death. The potential for physiologic addiction and potential withdrawal is also a significant risk. Symptoms of rapid benzodiazepine withdrawal include insomnia, anxiety, seizures, agitation, psychosis, retro-orbital pain, tachycardia, and death.<sup>53</sup> The starting dose of diazepam is 5 mg at nighttime to reduce the effect of sedation. The amount can be increased as tolerated to a maximum of 60 mg or more daily in divided doses. Peak blood levels are achieved in 1 hr after oral administration, and its half-life is 20–80 hrs. It is highly protein bound; thus, those with low serum albumin may experience more significant side effects. The partial benzodiazepine agent clonazepam has been used to treat nocturnal spasms and can be of value as an adjuvant agent in the treatment of spasticity.

### Novel Medications and Concepts

**Tetrahydrocannabinol.** In humans, there are two cannabinoid receptors. CB<sub>1</sub> is present in the peripheral and central nervous system, whereas CB<sub>2</sub> is expressed on immune cells. Cannabis also acts as an antagonist at N-methyl-D-aspartate receptors.<sup>54</sup> Given its N-methyl-D-aspartate antagonist effects, the synthetic cannabinoid dexabinol has been evaluated as a neuroprotectant agent in the treatment of traumatic brain injury. There are two agents presently available through prescription: dronabinol, the active alkaloid, and nabilone, the synthetic compound. Their approved uses include treatment of chemotherapy-induced nausea, human immunodeficiency virus-related wasting, and glaucoma.

Cannabis has been shown to decrease spasticity and tremor in an animal model of multiple sclerosis.<sup>55</sup> Persons with multiple sclerosis<sup>56,57</sup> and spinal cord injury<sup>58</sup> have re-

ported decreases in spasticity with the use of inhaled marijuana. In a double-blind, placebo-controlled trial, Ungerleider et al.<sup>59</sup> found that patients with multiple sclerosis reported less spasticity while receiving oral cannabinoids. However, no improvement was seen in a later study.<sup>60</sup> The pattern of spasticity may be important in predicting success of treatment; one study found the best response via clinical examination and electromyographic monitoring in those with primarily extensor tone.<sup>61</sup> The most recent evaluation of the use of cannabinoids in >600 people with multiple sclerosis demonstrated no improvement in Ashworth scale score but a subjective improvement in spasticity, discomfort, and mobility.<sup>62</sup> In a small study of a group of persons with spinal cord injury, the results were mixed.<sup>63</sup> The observed impairment of posture and balance seen in multiple sclerosis patients while under the influence of inhaled cannabis<sup>64</sup> may lead clinicians to use caution in prescribing oral cannabinoids in this population. However many of the proposed synthetic cannabinoids seem to remove most of the psychoactive effects. Dronabinol is given in 2.5- or 5-mg doses, which can be given in divided doses four times a day for a maximum daily dose of 20 mg/day.

**Glycine.** Glycine is one of the most abundant inhibitory neurotransmitters in the spinal cord and has been implicated in the mechanism of spinal shock.<sup>65</sup> In addition, in a murine model of congenital spasticity, a defect in the glycine receptor has been found.<sup>66</sup> Direct application of glycine or its agonists in mammals with spinal cord injuries results in decreased myotonia,<sup>67</sup> Hoffman reflexes,<sup>68</sup> and tone;<sup>68</sup> conversely, application of glycine antagonists increases tone.<sup>68</sup> Increased release of glycine has been implicated as a mechanism for the success of spinal cord stimulation in the treatment of spasticity.<sup>69</sup> Al-

though initial studies in the use of glycine as a treatment in humans show promise, they are limited to small sample sizes.<sup>70,71</sup>

Threonine, a glycine precursor, has also been studied as an antispasticity agent. In an early study of persons with spasticity of genetic origin, 12 mos of administration of 500 mg of threonine a day resulted in decreased symptoms.<sup>72</sup> A later study of higher doses of 4.5–6 g/day in a similar group of patients demonstrated improved objective findings, but no clinical improvement in spasticity.<sup>73</sup> Further studies with multiple sclerosis-related<sup>74</sup> and spinal<sup>75</sup> spasticity in doses of 6–7.5 g/day yielded similar results, with improvement in spasticity measures but limited symptomatic effect. No significant side effects were noted in any of the studies.

**Alpha Adrenergics.** Noradrenergic fibers are found throughout the central nervous system; in the spinal cord, they are located within the dorsal, ventral, and intermediate areas. Norepinephrine directly inhibits the action of spinal interneurons.<sup>76</sup>

Clonidine, although best known as an antihypertensive agent, has also been recognized as an antispasticity medication. Clonidine is a potent alpha-2 antagonist and also acts to inhibit release of glutamate. Its main method of action as an antispasticity agent is thought to be via alpha-2 presynaptic inhibition of sensory afferents,<sup>77</sup> although it additionally inhibits glutamate release. An early study in humans with particularly intractable spinal cord-related spasticity demonstrated promising results.<sup>78</sup> Administration of clonidine in six persons with spinal cord injury resulted in a significant reduction of the vibratory inhibition index.<sup>79</sup> However, in a comparison study, whereas clonidine, baclofen, and cyproheptadine all successfully reduced tone, clonidine demonstrated less reduction in the vibratory inhibition index of spinal cord-injured

patients.<sup>80</sup> Clonidine's effectiveness does not seem to be limited to spinal-related spasticity. Sandford et al.<sup>81</sup> reported good reduction in tone with clonidine in a person with a medullary infarct. A case series of patients with hypertonia due to a variety of cerebral pathogeneses also suggests clonidine's use for this population.<sup>82</sup> Clonidine has also been positively reported as an adjuvant agent with baclofen, despite the side effect of orthostatic hypotension.<sup>83</sup> Although outside the scope of this review, clonidine has also been used successfully in conjunction with baclofen in intrathecal administration for the treatment of painful sphincter spasms in spinal cord-injury patients.<sup>84</sup>

There are also some other intriguing effects that may make clonidine a good choice in persons with spinal cord injury. In 1982, Naf-tchi<sup>85</sup> reported restoration of motor and autonomic function in cats with chronic spinal cord injury after administration of clonidine. In a study of 12 humans with spinal cord injury undergoing partial-weight-supported treadmill training, the use of clonidine resulted in increased walking speed and improved posture.<sup>86</sup> In contrast with its success in persons with spinal cord injury, clonidine has been implicated in the slowing of neural recovery after brain insult in both animal models<sup>87</sup> and in humans.<sup>88</sup> As a result of these concerns, this agent may have greater utility with spasticity of spinal origin as opposed to that of cerebral origin.

Peak plasma levels of clonidine occur 3–5 hrs after oral administration, and its half-life is 5–19 hrs. The starting dose can be 0.1 mg/day. The transdermal form of clonidine has also been shown to be effective in controlling spasticity with minimal side effects.<sup>89,90</sup> Clonidine may produce hypotension, bradycardia, fatigue, dry mouth, and significant sedation.

Like clonidine, tizanidine also acts as an inhibitor of group II sensory afferents,<sup>91</sup> decreases the release

of excitatory neurotransmitters, and facilitates glycine. Its efficacy has been shown in the treatment of spasticity due to multiple sclerosis,<sup>92,93</sup> stroke,<sup>94,95</sup> spinal cord injury,<sup>96</sup> and brain injury.<sup>97</sup> In a multicenter trial of 142 multiple sclerosis patients with spasticity, tizanidine was shown to significantly decrease muscle tone, improve Ashworth scale scores and increase knee swing amplitude on pendulum testing compared with placebo. The improvements increased with elevated plasma concentrations.<sup>98</sup> In an earlier study by Emre et al.,<sup>92</sup> clinical and electrophysiologic responses had good correlation within individual patients' plasma levels, but poor correlation between patients, suggesting that medication dosing varies significantly between individuals. A good reduction in tone was seen in 30 persons with stroke-related spasticity; however, no effect was seen on strength of muscle force, tendon reflexes, or clonus.<sup>99,100</sup> In 17 patients with hypertonia due to traumatic brain injuries or strokes, tizanidine was found to improve Ashworth scores, tone control, and spasm scores and to increase motor strength in comparison with placebo.<sup>100</sup>

Tizanidine's utility is limited mostly by its side-effect profile; in a series of 47 persons with spasticity related to stroke, 89% were unable to tolerate the maximum daily dose due to adverse effects.<sup>98</sup> Commonly reported side effects include somnolence, asthenia, dizziness, dry mouth, and hypotension. However, studies comparing tizanidine with other agents suggest that it is better tolerated than baclofen<sup>99</sup> and diazepam.<sup>99</sup> Two meta-analyses examining the use of tizanidine in comparison with baclofen and diazepam in spasticity due to strokes, multiple sclerosis, and spinal cord injury found that tizanidine was less likely to weaken muscles.<sup>99,100</sup> Due to its similar mode of action to clonidine, the possibility of slowing neural recovery in persons with brain injury is

also a valid concern with tizanidine. The starting dose for tizanidine is 2–4 mg at bedtime, increasing to a maximum of 36 mg/day. A slow titration program is often best tolerated. Tizanidine's peak effect of 1–2 hrs is more rapid than clonidine, but its half-life is significantly shorter at 2.5 hrs.

**4-Aminopyridine.** 4-Aminopyridine is an agent first recognized as a potential treatment for ameliorating the effects of multiple sclerosis. It has been proposed to assist with transmission of the action potential over areas of demyelination by blocking the exposed potassium channels; however, more recent research in rat dorsal columns suggests that it improves speed of synaptic transmission and strength of muscle twitch.<sup>101</sup> In persons with spinal cord injury, 4-aminopyridine seems to improve central motor conduction and to increase cortical excitability.<sup>102</sup> Although studies of its utility in the treatment of multiple sclerosis have been inconclusive,<sup>103</sup> its utility in treating spasticity due to spinal cord injury is more convincing. Intravenous administration of single doses of 18–33.5 mg in spinal cord patients with incomplete injuries resulted in improvement in motor control and sensation and in a decrease in spasticity and pain; these effects lasted as long as 48 hrs.<sup>104</sup> However, these results were not seen in a later study examining electromyographic changes in similar intravenous dosages.<sup>105</sup> The enteral sustained release form, fampridine SR, has been shown to improve Ashworth scale scores in doses of 20–30 mg/day in persons with incomplete spinal cord injury, and further prospective evaluation of this agent is ongoing.<sup>106,107</sup> An additional benefit may be gained via improved pulmonary function.<sup>108,109</sup> Reported side effects include seizures, distal artery vasospasm, thrombocyto-

penia, increased liver enzymes, dizziness, and nausea.<sup>110</sup>

**Gabapentin.** Gabapentin is an agent whose use has extended well beyond its original indication for seizure disorder. Mueller et al.<sup>111</sup> first reported its success as an antispasticity agent in the multiple sclerosis population; in a placebo-controlled crossover trial of 15 multiple sclerosis patients with severe leg cramping, gabapentin use at 1200 mg/day resulted in improved Ashworth and Kurtzke scale scores. Lower doses of 300–400 mg/day also improved spasticity and disability in a later study.<sup>112</sup>

Gabapentin has also been shown to be efficacious in the spinal cord population; in 25 patients, dosages of 2400 mg/day were shown to decrease Ashworth scale scores by 11% and Likert scales by 20%.<sup>113</sup> Four of six spinal cord-injury patients showed electromyographic improvement with 1200 mg/day of gabapentin and even greater improvement clinically with 3600 mg/day.<sup>114</sup> No significant side effects were reported with any of the studies. Gabapentin's effectiveness has not been demonstrated in stroke- or traumatic brain injury-related spasticity; a case series of two patients with brain injury whose agitation was increased by gabapentin lends some concern to using it in this population.<sup>115</sup> Initial starting dose is 300 mg three times a day, increasing as tolerated to a 3600-mg maximum daily dose. It is generally well tolerated, but somnolence, dizziness, or ataxia can occasionally occur with its use. A study in persons with multiple sclerosis showed no worsening of concentration or fatigue when doses of 2700 mg/day were used.<sup>116</sup> Gabapentin is not metabolized through the liver, so it can be used in those with hepatic dysfunction.

**Alternative Agents.** Piracetam, a nootropic agent that has been used in the treatment of "vascular dementia," has been evaluated as an antispastic-

ity agent.<sup>117</sup> This agent seems to have a structure similar to GABA; however, cognitive side effects have not been prominent. In a study of 16 children with cerebral palsy, significant improvement was noted in about half of the children.<sup>117</sup> Progabide seems to act via both GABA<sub>A</sub> and GABA<sub>B</sub>. However, the development of this agent was limited by reports of liver toxicity.<sup>118</sup> Mondrup and Petersen<sup>119</sup> evaluated this agent in 16 patients with multiple sclerosis and hereditary spastic paraplegia. They noted improved spasm scores and preserved muscle strength in nonspastic muscles. Ivermectin has been reported as a potential antispasticity medication. The primary use of this medication is as an antihelminthic, and it is effective in the treatment of strongyloidiasis and onchocerciasis. It seems to act via GABA, and in a study of spinal origin spasticity, it was noted to improve spasms, with modest side effects noted.<sup>120</sup>

## Conclusion

Numerous enteral agents have been approved or are in the evaluation process for the treatment of spasticity. Although improvements in clinical measures of spasticity are noted with several of these medications, few have shown significant functional benefit. Perhaps these medications are best considered as agents to be used with other modalities to relieve symptoms and prevent complications. In the future, an ideal agent would have a limited side-effect profile, limited interaction, and deliver a targeted decrease in tone to only the affected muscle groups.

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