Pharmacological management of spasticity in Multiple Sclerosis: systematic review and consensus paper.

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ABSTRACT

Background and objectives: Treatment of spasticity poses a major challenge resulting from its complex clinical presentation and the variable efficacy and safety profiles of available drugs. We present a systematic review of the pharmacological treatment of spasticity in MS patients.

Methods: Controlled trials and observational studies were identified using MEDLINE and Cochrane databases. Scientific evidence was evaluated according to pre-specified levels of certainty. Practical considerations are provided for the different interventions considered.

Results: The evidence supports the use of baclofen, tizanidine and gabapentin as first line options for MS patients with spasticity. Diazepam or dantrolene could be considered if no clinical improvement is seen with the previous drugs. Nabiximols has a positive effect when used as add-on therapy in patients with suboptimal response or poor tolerance to first-line oral treatments. Despite methodological limitations in trials supporting their use, intrathecal baclofen and intrathecal phenol appear to show a positive effect in patients with severe spasticity and sub-optimal response to oral drugs. Local application of botulinum toxin or phenol injections can be beneficial in focal spasticity.

Conclusions: The available studies on spasticity treatment offer some insight to guide clinical practice, but are of variable methodological quality. Large, well-designed trials with better assessment tools are needed to confirm the effectiveness of antispasticity agents and to inform the design of evidence-based treatment algorithms.

BACKGROUND

Spasticity results from damage to the upper motor neurons of the corticospinal tract with abnormal supraspinal driving of spinal reflexes, and affects around 34% of multiple sclerosis (MS) patients.[1] It is characterized by increased muscle tone caused by hyperexcitability of the stretch reflex. It is often accompanied by weakness, pain and involuntary sudden movements (spasms) and, if severe, with contractures.[2] Patients with spasticity may exhibit worsening of symptoms in the setting of underlying infection, such as urinary tract infections, or other noxious stimuli.[3]

Different outcome measures are used to evaluate the degree of spasticity and its interference with function, including physician and patient-based scales.[4] The most widely used is the (modified) Ashworth scale, which provides a semi-quantitative measure of the resistance to passive movement graded from 0 to 5, as perceived by the examiner. Other scales in use are the (modified) Tardieu scale [5]; the Priebe and Penn scale[6] and self-reported scales such as the Visual Analogue Scale, the Numeric Rating Scale or the Multiple Sclerosis Spasticity Scale (MSSS-88)[7] which can address stiffness, clonus, spasms, pain and overall comfort. More complex techniques including the Wartenberg Pendulum tests, gait analysis or electromyography tend to be reserved for research purposes.[8]

Optimum management of spasticity requires a multidisciplinary team (physiotherapist, nurse, neurologist, rehabilitation physician) and regular follow up.[9] The goal of therapy is to increase functional capacity, facilitate rehabilitation, prevent contractures and relieve pain. The approach is usually multimodal, combining non-pharmacological and

pharmacological interventions.[10] An evaluation of the scientific evidence regarding physical therapy is beyond the scope of this review and detailed information can be found elsewhere.[11]

We aimed to (i) review the current literature involving pharmacological treatment of spasticity, (ii) offer advice on best use of available agents based on the evidence and the consensus of the expert authors and (iii) identify methological limitations in the available evidence.

METHODS (search strategy and consensus)

Evidence was collected by searches for systematic reviews, meta-analyses and original articles in MEDLINE and Cochrane databases before August 2013, using the search terms "multiple sclerosis", "spasticity", "spasm", "muscular rigidity", and their combinations, as well as abbreviations for the selected interventions (oral baclofen, tizanidine, dantrolene, benzodiazepines, gabapentin, cannabis-based drugs, botulinum toxin A, intrathecal baclofen and phenol injections). Additionally, the references of evaluated articles were screened for additional publications meeting the inclusion criteria.

We included controlled trials and observational studies involving patients with MS and spasticity of any degree. Studies in non-English languages, using non-validated or not specified outcome measures were excluded, as well as those studies involving patients with spasticity not due to MS (unless MS patients were at least half of the sample).We extracted information regarding efficacy and side-effects for each of the selected interventions.

Scientific evidence for antispasticity treatments was evaluated according to pre-specified levels of certainty (class I, II, III, and IV).[12] Due to the universal scope of this review, local issues such as costs and drug licensing were not taken into account when offering advice on use in clinical practice. Two independent investigators (SO and JS) evaluated the quality of evidence and wrote the initial draft that was evaluated by the chairman (XM) and circulated to the rest of the authors for further input, discussion and final agreement.

RESULTS

1. Centrally acting oral muscle relaxants

Oral baclofen

Oral baclofen is a structural analogue of gamma-aminobutyric acid (GABA) which crosses the blood-brain barrier and binds to pre- and postsynaptic GABA receptors, decreasing activity in motoneurons and interneurons. Control of symptoms is usually obtained with doses up to 60mg, with a maximum daily dose of 100mg.[13] Twelve controlled trials were identified and, after exclusion of two studies (lack of outcome description[14] and non-English language[15]), nine randomized[16-24] and one non-randomized[25] controlled trials met the inclusion criteria. Of these, seven were placebo-controlled trials[16;18;20;21;23;24;25] and three were comparations with diazepam[17;19;22]. Six out of the 7 placebo-controlled studies[16;18;20;23;24;25] showed a statistically significant improvement on spasticity when on baclofen compared with placebo, and one study, with a lower sample size, reported no differences[21] *(class II/III evidence).* Baclofen also improved the frequency of spasms and clonus[18;23] *(class III evidence).*

None of the three studies comparing baclofen and diazepam showed significant differences using the Ashworth or similar scales. [17;19;22] Similarly, there were no differences in the effect on the frequency of spasms between the two drugs[19;22] *(class III evidence).* One of these trials compared high versus low doses of baclofen (30 or 60 mg) and diazepam (15 or 30 mg).[17] While both doses showed a significant change in the Ashworth score before and after treatment, there was a marked improvement in those patients able to tolerate high doses *(class III evidence).*

In the majority of the analysed trials, baclofen showed an improvement in spasticity compared to placebo, with no differences compared to diazepam. However, the small size of the trials and the heterogeneity in the outcomes must be taken into account. Side effects, such as drowsiness, weakness, paresthesia, and dry mouth were common (10 to 75%) and limited the maximum tolerated dose, but they were fewer and better tolerated than those caused by diazepam.[26]

Tizanidine

Tizanidine is a short-acting muscle relaxant which stimulates the central alpha2-adrenergic receptors, leading to a reduced release of excitatory neurotransmitters at spinal and supraspinal levels. It is usually started at a dose of 2mg daily, increased up to a maximum dose of 36 mg daily with an average effective dose between 12mg and 24mg.[27] Thirteen trials met the inclusion criteria; two evaluating tizanidine in single dose compared with placebo[28;29] and 11 assessing the medium-term use of the drug (5–15 weeks) compared with placebo [30-33], with diazepam [34] or with baclofen[35-40].

The two single dose studies[28;29] showed significant dose-dependent improvement using the Pendulum test, but only the larger trial, involving 142 patients, showed an effect on the muscle tone *(Class II evidence).* The medium-term studies performed in the UK (187 patients) [33] and USA (220 patients) [31] evaluated treatment with tizanidine (titrated from 2 and 36 mg daily) compared to placebo over a 12 week period, using the Ashworth score. The UK study reported a significant reduction in muscle tone with tizanidine, while the USA study found no differences between groups. Both studies showed a greater, but nonsignificant, reduction in spasms and clonus in the treated group *(class I evidence).* It should be noted that the baseline muscle tone in the USA

study was slightly higher in the placebo group and its decrease was greater than expected.

In an additional placebo-controlled parallel trial (2-week washout period and a 3-week titration phase to a maximum dose of 32 mg per day) involving 66 MS patients, tizanidine showed a beneficial effect on spasticity without significant differences in the neurological status (Expanded Disability Status Scale –EDSS-)[32] *(class I evidence)*. In a further trial, testing sublingual and oral routes of administration, both had a positive effect compared to placebo in muscle tone, with no differences in walking speed (Timed 25-Foot Walk test) or fatigue (Fatigue Severity scale score). Sublingual tizanidine showed a significant reduction in the next-day somnolence (modified Epworth sleepiness scale)[30] *(class II evidence).*

When compared with baclofen or diazepam, tizanidine showed a similar positive effect with no statistical difference between treatment groups. Several outcomes were considered, such as muscle tone, frequency of spasms and clonus, neurological disability, functional disability, physician's assessment of clinical change and patient's subjective perception *(class II evidence)*[34-40].

In summary, tizanidine was superior in the short and medium term compared to placebo and equally effective compared to diazepam or baclofen. Side effects (mainly related to its alpha2-adrenergic activity including drowsiness and dry mouth) were dose-related. Decreases in blood pressure and heart rate were also reported, as well as transient increases in hepatic transaminase levels, with normalization following discontinuation of treatment.[41]

Benzodiazepines

Diazepam enhances the effect of the neurotransmitter GABA and suppresses neuronal activity in the reticular formation, contributing to muscle relaxation. The maximum recommended dose is 30 mg per day, with an average dose of 15 mg.[10] In the initial search, eight trials were identified and the only placebo-controlled trial[42] was excluded (only 4 out of 21 patients had MS). The remaining studies used baclofen[17;19;22], tizanidine[34], dantrolene[43] and ketazolam.[44;45] as active comparators.

As described previously, both diazepam and baclofen showed a positive effect on spasticity with a similar safety profile, despite more sedation observed with diazepam *(class III evidence)*[17;19;22]. When compared with dantrolene, tizanidine or ketazolam, diazepam also produced a similar reduction in spasticity *(class II/III evidence)*[34;43;44;45].

Gabapentin

Gabapentin is structurally similar to GABA, exerting GABAergic activity by binding receptors in the neocortex and hippocampus. The normal starting dose is 300 mg per day escalated up to a maximum daily dose of 3600 mg.[46] Five studies were identified and three were excluded for methodological reasons (open-label trials[47;48] and case report[49]). The analysed studies were randomized, placebo-controlled short-duration crossover trials.[50;51] The higher dose study[50] (up to 900 mg gabapentin orally three times daily over a 6-day period) reported a significant effect in all physician-assessed measures and subject-reported outcomes. The lower dose study[51] (400 mg gabapentin orally three times daily for 48 hours) also reported a decrease in the modified Ashworth score, but no effect on clonus, reflexes or response to noxious stimuli *(Class II*

evidence). The main adverse effects were drowsiness, somnolence and dizziness but it was generally well tolerated, with no serious side effects reported.[50;51]

Considering this evidence regarding centrally acting oral muscle relaxants, several practical recommendations can be made. In patients who experience spasticity, baclofen could be considered as one of the first treatment options. Due to the potential risk of dose related side effects, treatment should be initiated at low dose (5-10 mg daily) and gradually titrated upwards to a maximum of 100 mg per day.[13] Tizanidine may also be used as an alternative to baclofen, given the similarities in efficacy and global tolerability between both drugs. Dose related side effects and individual variation in the tolerated dose prove the need to start tizanidine at 2mg daily and slowly increase to a maximum of 36 mg. Given the risk of hepatic dysfunction, present recommendations include monitoring of liver function monthly for the first six months of treatment and periodically thereafter.[52] Gabapentin can be an alternative to baclofen and tizanidine, based on its clinical effect and safety profile, but no head to head comparations between gabapentine and other drugs are available. In light of the higher risk of side effects, diazepam could be considered in patients where no clinical improvement is seen with oral baclofen, tizanidine or gabapentin. The authors of this document agree that a step-wise approach to therapy favouring monotherapy is preferred to a combination of drugs. As inclusion criteria are not homogeneous in the available studies, the general indication would be to start treatment if there is interference with activities of daily living (basic and/or instrumental) or if the patient suffers from significant pain. See figure 1 for spasticity treatment algorithm.

2. Peripherally acting oral muscle relaxants

Dantrolene

Dantrolene acts on the contractile mechanism of skeletal muscle, decreasing the release of calcium. Treatment regimes are usually started at 25 mg once daily and increased gradually to a maximum of 400 mg divided into four doses.[53] Six studies were identified and three were excluded (open trial design[54] or MS patients representing less than half of the study sample[55;56]).

Two small studies, a crossover (20 patients)[57] and a parallel-group trial (23 patients)[58], compared dantrolene with placebo, starting at 50 mg or 25 mg four times a day, respectively, and titrated to a maximum of 100 mg. The crossover trial only provided patients' preferences (35% chose dantrolene over placebo, 20% preferred placebo and 45% had no preference)[57] *(class III evidence).* In the parallel-group study, a reduction in a spasticity semi-quantitative scale was observed in 42% of patients on dantrolene, and 27% on placebo[58] *(class III evidence).*

A later trial compared dantrolene versus diazepam using a fixed increasing dosage schedule over a two-week period, followed by another 2 weeks of maximum dose[43]. Both dantrolene and diazepam reduced spasticity and reflexes at low and high doses, but this reduction was significantly greater with dantrolene at higher doses. Subjective improvement was reported for two categories (muscle spasms or cramps and stiffness) with no statistical difference between drugs *(Class II evidence).*

Dantrolene proved superior to placebo using objective and subjective measures, based on low quality evidence. The usage of dantrolene is restricted due to the frequency of

side effects, such as gastrointestinal symptoms, weakness, fatigue, sedation and dizziness. The risk of hepatotoxicity is the major limitating factor and requires monitoring of liver function prior and during therapy.[53,59] As a consequence, the evidence would support the use of dantrolene only in patients where no clinical improvement is seen with oral baclofen, tizanidine or gabapentin (see figure 1 for spasticity treatment algorithm). Given that weakness is a frequent side effect, dantrolene may be reserved for non-ambulatory patients.

3. Cannabis-based drugs

Several pharmacological products with cannabinoid-receptor mediated effects containing D9-THC and cannabidiol (CBD) or synthetic D9-THC (dronabinol) are now available.[60] We identified 13 studies involving cannabis-based drugs for the treatment of spasticity in MS. Four were excluded (observational studies[61;62] a preliminary trial,[63] or MS patients representing less than half of the sample[64]) A total of 8 randomized placebo-controlled studies[65-72] and one metaanalysis[73] were considered.

The first available studies were a crossover trial using low doses of dronabinol (Marinol®) or a *C sativa* plant extract[66]; a large multicenter placebo-controlled trial (CAMS study, UK) using oral cannabis extract, delta9-tetrahydrocannabinol or placebo over 15 weeks[71] (and its subsequent follow-up study during 12 months[72]); and a single-centre placebo-controlled crossover study of cannabis-extract capsules containing tetrahydrocannabinol (THC) and cannabidiol (CBD).[69] They all used the mean change in the Ashworth score, showing no significant change at the end of the treatment period *(class II evidence).* However, they showed a significant improvement in spasticity, pain,

sleep disruption or spasms using self-completion questionnaires[66;69;71] *(class II evidence).* A significant treatment effect in the timed 10-meter Walk Test at 15 weeks (available for 278 out of the 630 patients) was seen in the CAMS study, but was no longer significant in the 12 month follow-up[72] *(class II evidence).*

Nabiximols (Sativex®) is an oromucosal spray of cannabis extract containing THC and cannabidiol. Therapy usually starts with a 2-week dose titration phase up to a maximum daily dose of 12 sprays.[74] Nabiximols was initially tested against placebo in MS patients with a variety of symtoms (spasticity, spasms, bladder problems, tremor or pain) evaluating the change in the Visual Analogue Score of their most troublesome symptom.[70] Patients on active treatment and spasticity showed a significant reduction in their Visual Analogue Score that could not be confirmed with the Ashworth scale *(class I evidence).* The Numeric Rating Scale was used as primary outcome in two further trials showing a significant improvement and highlighting the difference in the proportion of responders (defined as ≥ 30% reduction on the Numeric Rating spasticity score) between the nabiximols and placebo groups[75;76]*(class I evidence).* These three trials were combined in a meta-analysis, including 666 patients, that confirmed the overall eficacy of nabiximols.[73]

To overcome the possible underestimation of drug efficacy in previous studies, a recent trial used an enriched study design, selecting responders (at least 20% reduction in mean Numeric Rating score) in a single-blind study phase.[68] These patients were subsequently randomized in a double blinded phase to nabiximols or placebo over a 12 week period with a resulting significant superiority of nabiximols over placebo

according to the Numeric Rating Spasticity Scale. Nabiximols also had a better impact on spasm frequency, sleep disruption and the Barthel Scale[68] *(class I evidence).*

Finally, in a 5-week withdrawal study, patients on long-term treatment with nabiximols were blindly randomized to nabiximols or placebo.[67] Treatment failure (defined as either cessation of treatment, 20% increase in spasticity, or taking additional medication) was present in 94% subjects from the placebo group compared to 44% in the nabiximols group. The time to treatment failure significantly favoured nabiximols *(class I evidence).*

In summary, nabiximols showed a positive effect without serious adverse events in recent high class trials with an enriched study design, where it was used as an add-on therapy. However, there was an increased incidence of non-serious adverse events, with dizziness the most frequently reported.[77] This evidence would support its use in MS patients with spasticity and a suboptimal therapeutic response or poor tolerance to oral drugs (baclofen, tizanidine and gabapentin) (See figure 1 for spasticity treatment algorithm). The therapeutic response must be evaluated after 4 weeks, as only less than 50% of patients are responders, and discontinuation should be considered if no significant symptom improvement is seen. It is noteworthy that an influential review by NICE in the UK[78] accepted the data on nabiximols in terms of efficacy and safety. Their final recommendation that the drug not be used was made solely on grounds of its not meeting cost-efficacy requirements. We are aware that access to, and reimbursement of this drug, varies among healthcare systems more than others reviewed.

4. Peripherally acting injected muscle relaxants

Botulinum toxin

Botulinum toxin type A blocks release of acetylcholine at neuromuscular junctions inhibiting muscle contraction. Local injection of botulinum toxin A in isolated muscles has a lasting effect over several weeks with complete reversibility.[79] Five studies were identified in the initial search and three were excluded (case-series design,[80] MS patients representeing less than half of the sample[81] and open-label uncontrolled design[82]) .

Two placebo-controlled randomized trials were available.[83;84] Botulinum toxin (400 MU) tested in 10 chair-bound or bed-bound patients decreased the spasticity score and eased patient care[83] *(class III evidence).* The other trial evaluated three treatment arms (500, 1000 and 1500 MU) versus placebo on hip adductor spasticity.The modified Ashworth scale and spasm frequency improved to a similar extent in all four groups, but significant changes were only observed in muscle tone for the botulinum toxin groups. Time to re-treatment was significantly longer for all treatment doses compared with placebo *(class I evidence).*[84]

Only two trials evaluated Botulinum toxin in MS, involving a small number of patients over a short period of time. Nevertheless, the observed effects and the safety profile (similar to placebo with the exception of muscle weakness[84]), would support the use of local application of botulinum toxin A in patients with MS and focal spasticity of the lower limbs (see figure 1 for spasticity treatment algorithm). Botulinum toxin injection demands excellent knowledge of anatomy and function and physicians offering the treatment should be trained in its use. [79]

Local phenol injections

Phenol injected in motor points of selected muscles leads to axonal damage. Solutions between 5-8% phenol produce a selective effect, that can be maximized by combining phenol with glycerin which limits its spread.[85] No randomized controlled trials were identified evaluating the effect of phenol injections on spasticity due to MS or other causes. Given the lack of higher grade evidence, case series and observational studies were considered. Four studies were identified and two were excluded (lack of adequate description of the study population[86] and not adressing the topic of interest[87]). The remaining two studies were a case series[88] and a prospective study.[89]

The case series included 69 patients reporting a general relief of spasticity lasting from 3 to 14 months in the majority of patients *(class IV evidence).*[88] The prospective study included 62 patients followed over three months after phenol injection showing a significant reduction in the spasticity of hip adductors after the first week, with a maximum improvement after the first month. An important increase in the range of motion values for hip abduction was observed (*class IV evidence*).[89]

The evidence supporting the use of phenol injections for the treatment of spasticity is limited and of very low quality. Nevertheless, these studies showed a positive effect in reducing spasticity, spasms and pain in a high proportion of patients. Adverse effects were uncommon and temporary, with dysesthesia the most frequently reported. Therefore, phenol injections could be considered as an alternative to botulinum toxin in the management of focal spasticity, but higher quality evidence is needed to fully support its use.

5. Intrathecal therapies

Intrathecal baclofen

Since baclofen does not cross the blood-brain barrier effectively, intrathecal administration achieves much higher concentrations in the cerebrospinal fluid. A surgically implanted pump with reservoir allows four times the concentration of drug at 1% of the oral dosage. Pump implantation is considered only after testing responsiveness and optimal individual doses. Treatment is started at a dose of 25 µg per day, increasing over the first 6 months up to an average of 400 to 500 µg daily.[46]

Three randomized-controlled trials met the inclusion criteria[90-92] and all examined the effect of baclofen administered intrathecally by a programmable infusion pump after an initial screening stage to test responsiveness. In a long-term multicentre placebo-controlled trial including 22 patients, the active treatment group showed a significant improvement in the Ashworth score, the spasms score and the self-reported pain score (class I evidence) [91]. These results were confirmed in a larger multicentre trial[90] *(class III evidence)* and in a short-term placebo-controlled crossover trial[92] (class II evidence).

Intrathecal baclofen appears to show a beneficial clinical effect in patients with severe spasticity, accepting some limitations in the analysed studies including a failure to justify the sample sizes and a lack of published direct head-to-head comparisons. Side effects caused by the drug itself are uncommon, being drowsiness, dizziness, blurred vision and slurred speech the most frequently reported. Technical complications include those related to the surgical procedure, dysfunction of the pump and catheter-related issues.[90;93] The implantation of an intrathecal baclofen pump to relieve lower limb

spasticity could be considered if suboptimal response to oral drugs is observed. Prior to implantation, its efficacy must be evaluated by way of an intrathecal baclofen test and, in patients with walking ability this test must be performed using an external pump which allows the functional performance of the patient to be evaluated [94]. The authors of this document agree that a careful selection of patients based on the identification of realistic and mutually agreed treatment goals is recommended.

Intrathecal phenol

No randomized controlled trials evaluating the effect of intrathecal phenol on spasticity due to MS or other causes were identified and four observational studies were reviewed.[95-98] Two case series reported descriptive results in terms of general relief of spasticity *(class IV evidence).*[95;96] A cross-sectional observational study compared an initial phenol injection (initial group) versus subsequent injections (serial group) in five muscle groups, in both targeted and non-targeted sides, showing a significant reduction in the Ashworth score in both groups.[97] *(class IV evidence).* Finally, in a retrospective study, 40 patients treated with intrathecal phenol showed improvement using a simple rating scale and by attainment of rehabilitation goals *(class IV evidence).*[98]

Evidence supporting the use of phenol intrathecal injections is limited and of very low quality. This drug should be reserved for MS with severe spasticity and suboptimal response to oral drugs who do not show benefit after an intrathecal baclofen test, for which there is larger evidence to support its use. See Figure 1 for spasticity treatment algorithm.

CONCLUSIONS

Spasticity is a complex phenomenon resulting in a large inter- and intra-individual variability in the responses to therapeutic interventions. Overall, the methodological quality of the studies described was poor, with small sample sizes and short duration, which limits inference of long-term efficacy. There was also marked heterogeneity in patients' characteristics and treatment regimens. The difficulty in the quantification of spasticity is reflected in the wide variety of approaches taken to assess this symptom and in the global discrepancy between relief of spasticity and improvement of the neurological status. Furthermore, a discrepancy between published evidence and the daily experience of those who manage spasticity was also evident. There is a need for large, well-designed trials with better assessment tools that incorporate functional ability and patient's quality of life, to confirm the effectiveness of the widely used antispasticity agents.

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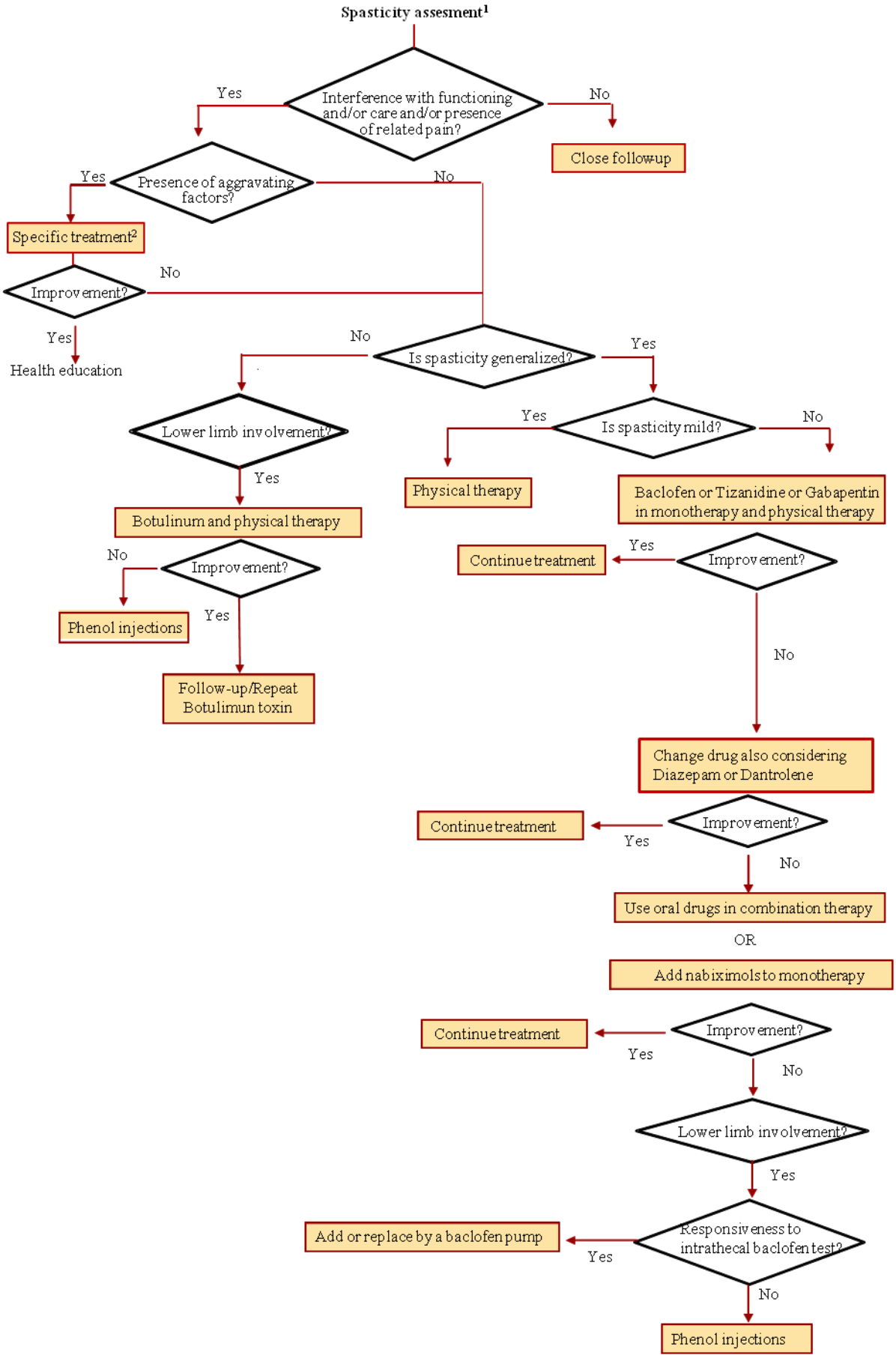
Figure 1. Spasticity treatment algorithm

1. Using validated scoring systems to determine the level of spasticity and evaluation of its impact on functioning. It is important to evaluate the beneficial and/or harmful effects of spasticity from a functional perspective as it is not always a disabling symptom/sign. In some cases, spasticity may have beneficial effects and improve the performance status of the patient.
2. Specific treatment of the aggravating factor (ie. antibiotics for urinary infection).

Adapted from: Clinical practice guideline on the management of people with Multiple Sclerosis[99]


Spasticity assesment[1]
Interference with functioning and/or care and/or presence of related pain?
Yes
No
Close follow-up
Presence of aggravating factors?
Yes
No
Specific treatment[2]
Improvement?
No
Yes
Health education
Is spasticity generalized?
No
Yes
Lower limb involvement?
Yes
Botulinum and physical therapy
Improvement?
No
Phenol injections
Yes
Follow-up/Repeat Botulimun toxin
Is spasticity mild?
Yes
No
Physical therapy
Baclofen or Tizanidine or Gabapentin in monotherapy and physical therapy
Improvement?
Yes
Continue treatment
No
Change drug also considering Diazepam or Dantrolene
Improvement?
Yes
Continue treatment
No
Use oral drugs in combination therapy
OR
Add nabiximols to monotherapy
Improvement?
Yes
Continue treatment
No
Lower limb involvement?
Yes
Responsiveness to intrathecal baclofen test?
Yes
Add or replace by a baclofen pump
No
Phenol injections