MANAGEMENT OF SPASTICITY IN MULTIPLE SCLEROSIS: A CONSENSUS STATEMENT OF THE HELLENIC NEUROLOGICAL SOCIETY, THE HELLENIC ACADEMY OF NEUROIMMUNOLOGY AND THE HELLENIC SOCIETY OF PHYSICAL AND REHABILITATION MEDICINE

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Abstract

Spasticity is a sensorimotor phenomenon characterized by velocity dependent hypertonia, involuntary muscle spasms or contractions, and is a common cause of disability and quality of life (QoL) impairment in multiple sclerosis (MS). Epidemiological evidence points towards a very high prevalence of MS-related spasticity (MSS) of up to 80% among MS patients. MSS is characterized by a wide spectrum of clinical manifestations and related complications, that contribute to worsening of motor deficits and loss of independence of MS patients, while if left without prompt treatment, MSS may lead to permanent joint deformities, muscle contractions, pain, involuntary movements, and skin complications. The diagnosis and clinical follow-up of MSS requires implementation of well-established clinical scales (Ashworth Scale, modified Ashworth scale, Tardieu Scale), but also requires use of functional scales that incorporate patient-relevant outcomes. The management of MSS should be initiated by multidisciplinary teams consisting of Neurologists and Physical Medicine and Rehabilitation (PM&R) physicians. Therapeutic goals include the overall clinical and functional improvement of the patient, the prevention of complications and contractures, as well as the facilitation of nursing and patient care. MSS treatments include non-pharmacological approaches such as rehabilitation sessions with specialized techniques, and pharmacotherapies, including administration of oral antispastics, intrathecal muscle relaxants, and intramuscular injections of botulinum toxin. The present consensus paper summarizes the current evidence on pharmacological and non-pharmacological MSS treatments, providing recommendations of an expert panel on the diagnostic approach and therapeutic management of MSS.

Key words: spasticity, multiple sclerosis, muscle relaxants, intrathecal baclofen, Botulinum toxin

ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΣΠΑΣΤΙΚΟΤΗΤΑΣ ΣΤΗΝ ΠΟΛΛΑΠΛΗ ΣΚΛΗΡΥΝΣΗ: ΚΕΙΜΕΝΟ ΟΜΟΦΩΝΙΑΣ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΝΕΥΡΟΛΟΓΙΚΗΣ ΕΤΑΙΡΕΙΑΣ, ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΑΚΑΔΗΜΙΑΣ ΝΕΥΡΟΑΝΟΣΟΛΟΓΙΑΣ ΚΑΙ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΦΥΣΙΚΗΣ ΙΑΤΡΙΚΗΣ ΚΑΙ ΑΠΟΚΑΤΑΣΤΑΣΗΣ

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Περίληψη

Η σπαστικότητα είναι μια αισθητικο-κινητική διαταραχή που χαρακτηρίζεται από μια εξαρτώμενη από την ταχύτητα υπερτονία και αποτελεί μια κοινή αιτία αναπηρίας και διαταραχής της ποιότητας ζωής (QoL) στην πολλαπλή σκλήρυνση (ΠΣ). Επιδημιολογικά στοιχεία υποδεικνύουν έναν πολύ υψηλό επιπολασμό σπαστικότητας σε έδαφος πολλαπλής σκλήρυνσης (ΣΠΣ) έως και 80% μεταξύ των ασθενών με ΠΣ. Η ΣΠΣ χαρακτηρίζεται από ένα ευρύ φάσμα κλινικών εκδηλώσεων και σχετιζόμενων επιπλοκών, που συμβάλλουν στην επιδείνωση των κινητικών ελλειμμάτων και στην απώλεια της ανεξαρτησίας των ασθενών με ΠΣ, ενώ χωρίς έγκαιρη θεραπεία, η ΣΠΣ μπορεί να οδηγήσει σε μόνιμες παραμορφώσεις αρθρώσεων, μυϊκές συγκάμψεις, πόνο, ακούσιες κινήσεις και δερματικές επιπλοκές. Η διάγνωση και η κλινική παρακολούθηση της ΣΠΣ απαιτεί την εφαρμογή καθιερωμένων κλινικών κλιμάκων (Κλίμακα Ashworth, τροποποιημένη κλίμακα Ashworth, κλίμακα Tardieu), αλλά απαιτεί επίσης τη χρήση λειτουργικών κλιμάκων που ενσωματώνουν παραμέτρους σημαντικές για τον ασθενή. Η διαχείριση της ΣΠΣ θα πρέπει να συντονίζεται από διεπιστημονικές ομάδες που απαρτίζονται από Νευρολόγους και ιατρούς Φυσικής Ιατρικής και Αποκατάστασης. Οι θεραπευτικοί στόχοι περιλαμβάνουν τη συνολική κλινική και λειτουργική βελτίωση του ασθενούς, την πρόληψη επιπλοκών και συγκάμψεων, καθώς και τη διευκόλυνση της νοσηλευτικής φροντίδας του ασθενούς. Οι θεραπείες της ΣΠΣ περιλαμβάνουν μη φαρμακολογικές προσεγγίσεις όπως συνεδρίες αποκατάστασης με εξειδικευμένες τεχνικές, και φαρμακοθεραπείες, συμπεριλαμβανομένης της χορήγησης από του στόματος αντισπαστικών, ενδορραχιαίων μυοχαλαρωτικών και ενδομυϊκών ενέσεων αλλαντοτοξίνης. Το παρόν άρθρο ομοφωνίας συνοψίζει τα επιστημονικά δεδομένα σχετικά με τις φαρμακολογικές και μη φαρμακολογικές θεραπείες της ΣΠΣ, παρέχοντας συστάσεις μιας ομάδας ειδικών αναφορικά με τη διαγνωστική προσέγγιση και τη θεραπευτική διαχείριση της ΣΠΣ.

Λέξεις ευρετηρίου: σπαστικότητα, πολλαπλή σκλήρυνση, μυοχαλαρωτικά, ενδορραχιαία βακλοφαίνη, βοτουλινική αλλαντοτοξίνη

ΕΛΛΗΝΙΚΗ ΝΕΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

1. Introduction

Multiple sclerosis (MS) comprises the most frequent inflammatory and neurodegenerative demyelinating disorder of the human central nervous system (CNS) [1]. Spasticity is a common cause of disability and quality of life (QoL) impairment in MS, with epidemiological evidence pointing towards a very high prevalence of MS-related spasticity (MSS) of up to 80% among MS patients [2-4]. MSS can be clinically defined as a type of hypertonia (involuntary muscle contraction), that presents with increased, speed-dependent resistance to stretching of skeletal muscles [5]. The underlying pathophysiological mechanisms of MSS are related to demyelinating lesions in the brain or spinal cord, that precipitate neuronal dysfunction and secondary axonal degeneration of descending corticospinal and/or rubro-/reticulospinal tracts, which result into disturbed inhibitory interneuronal spinal pathways and velocity-dependent increase of muscle tone [6, 7].

MSS is characterized by a wide spectrum of clinical manifestations. In MS patients, MSS manifests typically with concomitant "positive" upper motor neuron (UMN) signs, including clonus, co-contraction of antagonist muscles, and abnormal reflexes, and also with "negative" signs, including loss of coordination, weakness and fatigability of affected muscles (Table 1) [2, 8]. In the context of UMN syndrome, MSS results in motor impairment, as well as gait and balance impairment, limiting ambulation and functional independence of MS patients [9]. MSS can manifest clinically either in a tonic or a phasic form (i.e., with continuously or intermittently increased muscle tone, respectively), causing painful muscle spasms, which in turn precipitate sleep disorders and neuropsychiatric complications in MS patients [6]. Additionally, MSS may cause bladder dysfunction as a result of detrusor muscle and external urethral sphincter (spastic muscle) dyssynergia, resulting in detrusor overactivity with urinary incontinence, urinary retention (with mixed symptoms being the most predominant) and dysuria [10]. MSS may also result in bowel dysfunction by adversely affecting the function of muscles of the gastrointestinal tract/pelvic floor [11]. Notably, MSS is also implicated in the manifestation of dysphagia in MS patients [12]. Moreover, chronic spasticity may result in muscle shortening and limb deformities that contribute significantly to the deterioration of patient functional status [2]. MSS is thus, a complex phenomenon, and one of the major causes of disability in MS with negative impact on QoL and MS prognosis [8].

In fact, despite the tremendous advances in the development of immunomodulatory therapies for MS during the last years, a significant proportion of MS patients still experience moderate to severe MSS-related disability [2-4]. Early-implementation of targeted pharmacological and non-pharmacological treatments for MSS is thus, of paramount importance. Such interventions aim to improve QoL through preservation of mobility and functional independence, pain alleviation, and facilitation of nursing [6, 13]. In addition, because of the rising global incidence of MS as well as the increasing survival rates of MS patients [14, 15], MSS has been linked to increasing healthcare costs with detrimental implications for individual patients and healthcare systems worldwide [16]. There is consequently, an urgent need to raise awareness among clinicians regarding the necessity of early recognition and management

Table 1. Positive and negative signs of upper motor neuron syndrome (UMN)

Positive signs	Negative signs
Flexor and extensor muscle spasms	Fatigability
Clonus	Incoordination
Automatisms	Atrophy
Increased deep tendon reflexes	Lack of strength
Rigidity	Lack of motor control
Dystonia	Impaired fine movements
Athetosis	
Spasticity	
Spastic dystonia	
Babinski sign	
Primitive reflexes	
Muscle synergies	

Table 2. Clinical characteristics for the differential diagnosis of spasticity

Spasticity	• Lesions in the pyramidal tract or in vestibulo-/rubro-/ reticulospinal tracts • Velocity – dependent, also length-dependent in MS • Mainly affects muscles resisting gravity, in MS mostly in lower extremities • More resistance in one direction • Clasp knife phenomenon (more tone in the initial phase of movement)
Dystonia	• Involuntary, sustained or intermittent muscle contractions • Twisting or repetitive movements/ abnormal postures
Intrinsic hypertonia	• Soft tissue changes and overactivation of spindle afferents • Same resistance in all directions • Velocity independent
Spastic dystonia	• Uncontrolled muscle contractions, abnormal postures • Simultaneous activity of both agonist and antagonist muscle groups

of MSS, as well as a pressing need to establish interdisciplinary teams for optimal care of MS patients.

The present consensus paper of the Hellenic Neurological Society, the Hellenic Academy of Neuroimmunology and the Hellenic Society of Physical and Rehabilitation Medicine summarizes the current evidence on pharmacological and non-pharmacological MSS treatments, providing recommendations of an expert panel on the diagnostic approach and therapeutic management of MSS.

2. Definition and pathophysiology of MSS

Lance proposed in 1980 the more systematic definition of spasticity as "a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the UMN syndrome" [17]. Beyond the association of spasticity with UMN syndrome, Young expanded the definition of "spastic paresis" to include the presence of "extensor plantar responses, velocity-dependent increase in tonic stretch reflexes, exaggerated phasic stretch reflexes, increased autonomic reflexes, and abnormal postures" [18]. More recently, sensory aspects of spasticity have been acknowledged [19], which have contributed to our current understanding of spasticity as a sensorimotor phenomenon, associated with automatic movement responses to sensory inputs [8]. Spasticity is thus, defined as "a disorder of sensorymotor control caused by UMN lesions that manifests as intermittent or sustained activation of muscles" [20]. Accordingly, MSS occurs as a consequence of involuntary stimuli to muscle tissue to contract [21].

In patients diagnosed with MS [22, 23], CNS injury results in loss of descending inhibitory pathways and in increased excitability of dynamic gamma neurons and alpha motor neurons, that cause aberrant muscle activation [24]. Additional spinal tracts, including vestibulospinal and rubro-/reticulospinal pathways, may be overtly activated contributing to the disinhibition of stretch reflexes. MSS thus, arises as a consequence of CNS lesions and secondary neuroplastic changes, that induce an imbalance of supraspinal inhibitory and excitatory inputs directed to the spinal cord [7].

Even though MSS manifests as a consequence of neuroplastic adaptation to lesions of corticospinal or vestibulo-/rubro-/reticulospinal tracts, these neuroplastic changes lead to secondary effects on the neuromuscular system [7, 25]. Such effects include soft tissue changes (i.e., in muscles, tendons, and ligaments) and muscle contractures causing overactivation of spindle afferents, which in turn aggravate MSS. In contrast to the velocity-dependent MSS, muscle hypertonia due to soft tissue changes manifests clinically with increased resistance to passive movement of skeletal muscles that is not velocity-dependent, and is often referred to as non-reflex hypertonia or intrinsic hypertonia (Table 2) [26-28].

Clinically, besides the distinction of MSS from intrinsic hypertonia, it is important to differentiate MSS from dystonia, which refers to involuntary, sustained or intermittent muscle contractions, that cause twisting, repetitive movements, or abnormal postures (Table 2) [5]. Additionally, in MS patients, overlapping syndromes may occur, which include spastic dystonia that refers to the inability of a muscle to relax leading to spontaneous tonic contraction [29], and spastic co-contraction that implies the simultaneous activity of both agonist and antagonist muscle groups and is particularly profound in spastic paresis [8, 30]. We should also refer to the paroxysmal components of spastic dystonia, as they are of particular relevance for the treatment of spasticity in MS patients [31].

Concerning the evolution of spasticity over time, the pathophysiological correlates and course of spasticity are less well-characterized in MS compared

to other neurological disorders associated with spasticity, including stroke. In stroke, for example, a time-dependent manifestation of spasticity is described, with increasing prevalence of spasticity with increasing time from stroke onset: affecting 4-27% of patients in the early post-stroke period (1-4 weeks poststroke), 19-27% in the post-acute phase (1-3 months poststroke), and 17% to 43% of those in the chronic phase (>3 months poststroke) [32]. Due to several variables contributing to the development of MSS, its evolution over time is difficultly to assess in observational studies. Nonetheless, MSS is thought to follow a similar pattern of progression, occurring with a latency of weeks to months after a CNS insult, and typically reaching its clinical peak between 3 and 6 months following a clinical event [33]. Importantly, there is a significant correlation between MSS and disease duration, as well a significant association between MSS and progressive courses of the disease [33].

3. Clinical characteristics of MSS

With regard to the clinical features of MSS, it should be emphasized that MSS manifests not only as a velocity-dependent, but also as a length-dependent phenomenon [7]. For example, in the quadriceps muscles, greater spasticity is noted when the muscle is shorter (i.e., in the slightly flexed knee position) compared to when the muscle is longer (i.e., when the knee is fully flexed), a mechanism possibly underlying the so-called "clasp-knife" or "catch" phenomenon [34]. Conversely, in the upper limb flexors and ankle extensors (triceps surae), spasticity is greater when the muscle is longer [35, 36].

With respect to MSS distribution, it should be noted that MSS most frequently affects the flexor muscles in the upper limb and the ankle plantar flexors in the lower limbs [7]. Interestingly, a phylogenetic advantage associated with the preservation of human standing posture is thought to underlie this distribution of spasticity, as indicated by the fact that muscles resisting gravity are the ones most commonly affected in patients with UMN syndrome [28].

Another important feature of MSS is that, although MS can affect all levels of human CNS, the probability of impairment of a functional pathway is higher with increasing pathway length [27]. This observation has been confirmed by independent studies demonstrating a higher prevalence of MSS in the lower compared to the upper limbs of MS patients [37, 38]. For example, in an electrophysiological study including 59 MS patients, MSS was present in ankle extensors in 85%, in knee extensors in 44%, in knee flexors in 32%, in wrist flexors in 10%, in elbow flexors in 8%, and in elbow extensors in 3% of the patients [38]. In clinical practice, hip adductors are also predominantly affected in MS patients, limiting passive mobilization and affecting significantly patient care and hygiene.

According to the anatomical distribution, MSS can be classified as focal, multifocal, segmental, generalized spasticity and hemispasticity [39]. Focal and multifocal spasticity affect one and ≥2 non-contiguous body regions, respectively. Segmental spasticity affects ≥2 contiguous body regions. **Generalized spasticity affects** the trunk and ≥2 additional sites. In line with the previous definitions, a paraspasticity should be classified as a segmental and a tetraspasticity as a generalized spasticity form.

As indicated by the complex definitions, clinical presentations and classification schemes that were previously analyzed, it is difficult to approach spasticity in clinical practice without the use of standardized clinical assessment tools. Importantly, the implementation of clinical scales facilitates not only the clinical diagnosis and early-recognition of MSS, but also the conduction of epidemiological research in the MS patient population.

4. Clinical scales for MSS assessment

MSS is assessed in clinical practice using semi-quantitative scales, such as the Ashworth Scale (AS), the modified Ashworth Scale (MAS) and the Tardieu Scale (Table 3), which are based on the degree of resistance to passive movement of different body segments as perceived by the examiner, or by neurophysiological investigations such as the H-reflex and the Wartenberg pendulum tests, the latter being mostly used in research [40-45]. The REsistance to PAssive movement Scale (REPAS) has been developed from AS, requiring standardization of the clinical examination, and is thus, characterized by a higher reliability regarding spasticity assessment in different muscle groups [46]. Moreover, since MSS predominantly affects the hip adductors, standardized assessment of passive hip abduction (i.e., using protractor goniometer), measurement of the maximum distance between the knees during passive abduction and use of the Adductor Tone Rating Scale (ATRS) are recommended [47].

In clinical practice, there are four stages of clinical examination, including static and functional evaluation [48). *Stage 1*: Clinical observation - The image presented by the patient's body as they enter the examination room and when in a sitting and supine position. Any muscular atrophies and/or muscular spasms are also recorded. *Stage 2*: In a supine position the examination includes the range of joint motion with passive slow movement; the spasticity degree; the active movement; and the normal and pathological reflexes. At this stage we use the motor test, the MAS, the ATRS, and the Tardieu Scale. *Stage*

Table 3. Clinical scales for spasticity assessment

GRADING	SCALES			
		Ashworth	**Modified Ashworth**	**Modified Tardieu**
	0	No increase in muscle tone	No increase in muscle tone	No resistance throughout the passive movement
	1	Modest increase in tone giving catch in flexion and extension	+ catch and release or minimal resistance at the end of the range of motion	Modest resistance through the passive movement
	1+	–	+ catch followed by minimal resistance through the remainder of the range of motion, easy motion	–
	2	More noticeable increase in tone, but the limb is easily flexed	+ through most of the range of movement, easy motion	Clear catch at a specific angle, interruption of passive movement, followed by release
	3	Significant increases in tone, passive movement difficult	Significant increases in tone, passive movement difficult	Fatigable clonus (<10s with stable pressure), at a precise angle
	4	Limb rigid in flexion or extension	Limb rigid in flexion or extension	Unfatigable clonus (>10s with stable pressure) at a precise angle
	5	–	–	Fixed joint

Velocities' definition (according to modified Tardieu scale)	
V1	Very slow (slower than the limb drop under gravity)
V2	Same velocity as the limb falling under gravity
V3	Faster than the natural drop

3: Examination with the patient in a sitting position. Here the examination is supplemented by an upper limb motor skill test. *Stage 4*: Examination of body balance in upright position and walking for a short and longer distance. Fatigue is considered as a major factor of movement disturbance [48].

An overview of 24 clinically-used scales for measuring spasticity can be found in Platz et al. [41]. This systematic review showed that the methods most frequently used for the assessment of spastic muscle tone are the AS and MAS scales. These scales are easy to implement, but show varying degrees of interrater reliability across studies [41]. Besides the significant interrater variability, additional limitations of these scales comprise the lack of assessment of patients' MSS experience and the fact that none of these scales is designed to reflect how MSS affects patients' daily lives [49].

Patient-reported outcomes are thus, used both in clinical practice and research, including the Numerical Rating Scale (NRS), the Visual Analogue Scale (VAS) and the Multiple Sclerosis Spasticity Scale (MSSS-88) (Table 4) [40, 49]. Further assessment methods and QoL measuring instruments ("patient-related outcome measures, PROMs" and "health-related quality of life measures, HRQL") can also be implemented [50, 51], including: active and passive range of motion in motion segments (aROM, pROM), 10 m walking time, disability assessment scale (DAS), and Goal Attainment Scale (GAS) [52-55]. The GAS in particular, utilizes six goal areas under two domains: (a) body structure impairment: pain, involuntary movements, and range of movement and (b) activities/function: passive function (ease of caring), active function –transfers or standing, and active function– mobility, to evaluate achievement of treatment goals [56].

In clinical practice, it is advisable to monitor responsiveness to MSS therapies using both clinically standardized (AS scale, MAS, Tardieu, or REPAS scale) and functional scales, that incorporate patient-relevant symptoms and treatment-goals [51]. Nonetheless, it should be mentioned, that there is lack of consensus

Table 4. Overview of clinical scales and tools for patient-reported outcome assessment in MS patients with spasticity-related symptoms

Parameter	Tool	Characteristics
Tonus	REPAS, (modified) Ashworth Scale, (modified) Tardieu Scale, Numerical Rating Scale (NRS)	High inter-rater variability, low sensitivity regarding moderate changes
Paresis	BMRC-Grading of Muscle Strength	Assess in supine or resting position
Spasms	Spasms Frequency Rating Scale, Penn Spasm Frequency Scale	Variation during day
Pain	Visual Analogue Scale (VAS)	Useful to monitor treatment
Joint Mobility	Neutral Zero Method, Range of Movement	Useful for assessment of joint deformities or muscle contractures
Walking speed	10-meter walking test, 25-foot walking test	Easy to perform
Walking Distance	EDSS (ambulation)	Variation during day
Endurance	2-minute walking test (2MWT) 6-minute walking test (6MWT)	Easy to perform, highly reproducible
Daily walking distance	Pedometer or Accelerometer	Highly sensitive for clinical deterioration
Everyday Relevance	MSSS-88	Useful for evaluation of spasticity impact on daily activities

Abbreviations: REPAS: Resistance to Passive Movement Scale, BMRC: British Medical Research Council scale for muscle strength, EDSS: Expanded Disability Status Scale, MSSS-88: The 88-item Multiple Sclerosis Spasticity Scale.

on whether a particular combination of scales is superior to others. The use of variable tools for evaluating MSS limits the comparability of results obtained from different clinical trials and observational studies (e.g., on the efficacy of antispastic agents on MSS). Therefore, in clinical practice, the use of the same combination of scales is advisable for the follow-up of MS patients [57, 58].

5. Epidemiology of MSS

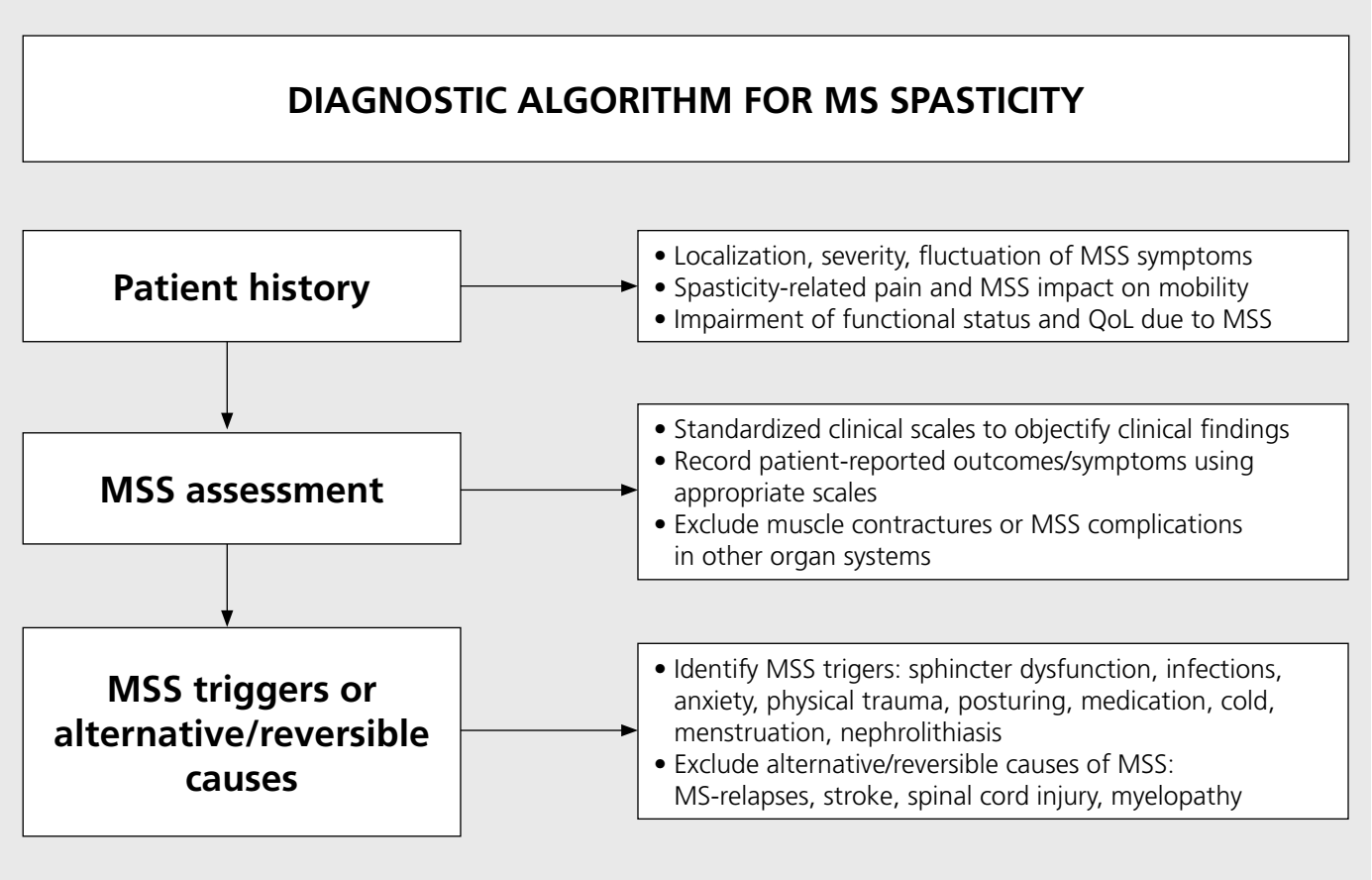
As noted in previous sections, the use of clinical scales for the evaluation of MSS is a prerequisite for the performance of epidemiological research in the MS patient population. Evidence from large epidemiological studies indicates that MSS is present in up to 80% of MS patients, while nearly all patients with progressive types of MS exhibit some degree of MSS [3, 4, 59]. In addition, approximately one third of MS patients suffer from moderate/severe MSS despite antispastic treatments [4, 33, 60], eliminating, thus, their daily activities [45, 59]. Several observational studies have shown that daily life is mostly affected as a consequence of motor impairment or MSS-related limb stiffness [61, 62].

Epidemiological evidence points toward an increasing incidence of MS in the Greek population during the last decades. The mean annual incidence rate of MS increased from 2.71/100,000 recorded during the period 1984-1989 to 10.73/100,000 in the 5-year period of 2002-2006 [63, 64]. Accordingly, Greece belongs to the high-risk geographical areas for MS [64]. In addition, electrophysiological evidence suggests a particularly high incidence of MSS among patients with progressive types of MS [65]. Interestingly, Greek observational studies indicate that MSS is frequently complicated by vesicourethral dysfunction, muscle spasms, pain and functional impairment in MS patients [66, 67].

With respect to risk factors, the presence of severe paralysis, sensory deficits, and pain have been linked to increased risk of spasticity [32, 68]. Crucially, MSS-aggravating factors (so-called spasticity triggers) have been identified specifically in MS patients, including immobility, pain, noxious stimuli, emotional tension, infections, urge to stool/urinate, pressure ulcers, thromboses and fractures [40, 69, 70].

While early-recognition of risk factors is pivotal for MSS therapy, it should be stressed that in accordance with the "NEDA" principle (No Evidence of Disease Activity) [71-73], the early implementation of disease modifying therapies (DMTs) for MS and the regular re-evaluation of indications to escalate DMTs comprise the cornerstone of MS but also MSS treatment [74]. Crucially, several studies corroborate the positive effect of DMTs on MSS progression [58], while vice

Figure 1. Diagnostic algorithm for multiple sclerosis spasticity



Abbreviations: MS: multiple sclerosis, QoL: quality of life, MSS: multiple sclerosis-related spasticity

versa MSS progression and accumulation of disability are linked to disease activity [75]. On the other hand, interferons have been reported to aggravate MSS [58, 76, 77], a fact that should be considered when prescribing DMTs in MS patients [58].

Furthermore, the effect of some antidepressants should be monitored closely in patients with MSS, since previous studies indicate that selective serotonin reuptake inhibitors may exacerbate MSS [78, 79], presumably due to serotonin effects on the motor neuron and reflex activity [78]. In addition, some anecdotal reports suggest a possible link between spasticity and antiepileptic drugs, such as lamotrigine [80]. Although associations between concomitant medication and MSS are poorly-characterized, regular assessment for potential drug-induced triggers of MSS is recommended, using patient-reported measures of MSS as described in previous sections [81].

6. Diagnostic and therapeutic approach to MSS

The initial approach of patients with MSS entails thorough assessment of their medical history. Besides the exclusion of potential triggers that may aggravate spasticity, concomitant disorders that may contribute to MSS should be explicitly evaluated (Figure 1). For example, MS patients are known to harbor an increased risk for cerebrovascular disease that may contribute to MSS; thus, assessment of presence of concomitant cerebral small vessel disease and cardiovascular risk factors is pivotal [82-84]. Moreover, as bladder dysfunction in MS patients is very frequently complicated by urinary tract infections, prompt recognition and management of underlying urinary tract infections that may aggravate MSS is essential [10]. Besides history taking and clinical evaluation, ancillary testing may be indicated, including neuroimaging studies, neurophysiological studies, cerebrospinal fluid (CSF) analysis, laboratory or genetic/molecular testing in order to exclude other neurological diseases (e.g., progressive multifocal leukoencephalography in patients under DMTs, myelopathy, and hereditary spastic paraplegia among others) that could complicate or mimic MS, resulting in MSS [85-88]. Moreover, as discussed in previous sections, the diagnosis of MSS should include detailed assessment of different functional domains, including use of Multiple Sclerosis Functional Com-

Table 5. Overview of non-pharmacological interventions for MS-related spasticity (MSS)

Non-pharmacological treatment	Level of evidence
Physical exercises (except sports climbing with no evidence): muscle strengthening, stretches, balance exercises, gait training, endurance exercises, hydrotherapy, electronic bike training, robotic-assisted rehabilitation and virtual reality programs	Low, expert consensus to recommend for MSS
Occupational therapy, logotherapy, nutrition monitoring to prevent muscle wasting and osteoporosis, and psychological support	Low, expert consensus to recommend for MSS
Intermittent Theta Burst stimulation (iTBS), Repetitive Transcranial magnetic stimulation (rTMS)	Low, expert consensus to recommend for MSS
Transcranial direct current stimulation (tDCS)	No evidence of efficacy, not recommended for MSS
Transcutaneous electrical nerve stimulation (TENS)	No evidence of efficacy, only in selected patients
Whole body vibration (WBV)	No evidence of efficacy, not recommended for MSS

posite (MSFC) and Expanded Disability Status Scale (EDSS), and different organ systems, while taking into account potential complications of MSS, including bladder/bowel dysfunction, dysphagia, contractures and limb deformities, as well as pressure sores [2, 11, 12, 89-91].

Crucially, the therapeutic management of MSS should be individualized, while focusing on the establishment of treatment-goals collaboratively with patients, their carers and rehabilitation teams, prior to initiation of MSS treatment [92]. Clinically-relevant goals of MSS treatments include: improvement of motor performance, ambulation and functional disability; pain reduction; facilitation of nursing; and prevention of complications, such as contractures and pressure sores [6, 40, 48, 51]. Notably, MSS therapy should be provided by multidisciplinary teams, including neurologists, physical medicine and rehabilitation physicians, nurses, physiotherapists, speech therapists and other allied specialties, while typically, combination of different treatment modalities and rehabilitation techniques is warranted for optimal patient care [93-95]. In brief, MSS therapies encompass non-pharmacological therapies, including physical therapy, magnetic and electrical stimulation and peripheral nerve stimulation, and pharmacological therapies, including oral antispastic drugs, muscle injections with botulinum neurotoxins, and intrathecal administration of anti-spastic drugs, which will be separately presented in the following sections [6, 40].

7. Non-pharmacological therapies for MSS

Non-pharmacological interventions may be used alone or in combination with pharmacological agents to treat MSS [92]. To date, there is a striking gap in the scientific literature concerning optimal non-pharmacological treatments for MSS, as robust data from large, well-designed randomized-controlled clinical trials (RCTs) are scarce [96]. A systematic Cochrane review, summarized the available evidence on non-pharmacological treatments of MSS and compared them with any type of control intervention in adult MS patients [92]. The authors identified nine RCTs comprising 341 patients, which investigated various types and intensities of non-pharmacological MSS interventions. Among the studied interventions were: physical activity programs (including physiotherapy, structured exercise program, sports climbing); transcranial magnetic stimulation [intermittent Theta Burst Stimulation (iTBS), repetitive Transcranial Magnetic Stimulation (rTMS)]; transcranial direct current stimulation (tDCS), Transcutaneous Electrical Nerve Stimulation (TENS) and Whole-Body-Vibration (WBV). Notably, due to the high heterogeneity of included RCTs, a meta-analysis could not be performed, whereas further limitations of RCTs included small sample sizes, high risk of bias, short follow-up periods, variable outcome measures, and inclusion of diverse MS patient populations with diverse MSS symptoms. In particular, the authors reported that all studies scored 'low' on methodological quality assessment [92].

This systematic review concluded that there was 'low level' of evidence for physical activity programs used in isolation or in combination with other interventions for MSS (pharmacological or non-pharmacological), as well as 'low level' of evidence for intermittent/repetitive magnetic stimulation (iTBS/rTMS) with or without adjuvant exercise therapy to improve MSS in adults [92]. Conversely, no evidence of benefit was detected to support the use of TDCS, TENS, sports climbing and vibration therapy for MSS treatment (Table 5).

7a. *Physical activity programs*

With respect to physical activity programs, the

previous systematic Cochrane review [92] included 4 RCTs [97-100] that evaluated the impact of different types of physical therapy (including structured physiotherapy, exercise program and sports climbing) on MSS. Among them, 3 RCTs evaluated these therapies in conjunction with other interventions: botulinum neurotoxin (BoNT) [97], iTBS [98], and vibration therapy [99]. One RCT [97] with 38 secondary progressive MS patients, examined whether the addition of physiotherapy may enhance BoNT's efficacy in treating focal spasticity. The intervention group received BoNT and add-on daily physiotherapy for 15 days, encompassing passive, active and stretching exercises, while the control group received only BoNT. This RCT found a significant decrease in MSS in the combination treatment group compared to the group receiving only BoNT injections, as indicated by the significant reduction in MAS scores noted for up to 12 weeks following treatment. Another double-blind, sham-controlled clinical trial [98] investigated the effects of combined iTBS and exercise therapy on motor disability in MS patients. Thirty patients were randomized into 3 groups: iTBS plus exercise therapy, sham stimulation plus exercise therapy, and iTBS alone. There was a significant improvement in MAS scores, MSSS-88, fatigue and QoL scores in the iTBS plus exercise therapy group, but not in the sham stimulation plus exercise therapy group. A significant reduction in MAS score was also noted in the iTBS group, while other measures of MS-related disability remained unaffected in this treatment group. One trial [99] evaluated the efficacy of WBV on muscle tone, muscle force, sensation and functional ability in MS. Sixteen participants were randomly allocated into two groups: the first group underwent 4 weeks of WBV plus exercise 3 times per week, 2 weeks of no intervention and then 4 weeks of exercise alone 3 times per week; the second group underwent these treatment interventions in the reverse order. The exercise program had positive effects on muscle force and well-being, but there was insufficient evidence that the addition of WBV provided any additional benefit, while no significant differences in MAS scores were detected from either intervention. Nevertheless, for each group, the combination of WBV with exercises showed significant reductions on MSSS-88 sub-scales of muscle spasms and pain. Some non-significant improvements in functional abilities were also noted, including 10-meter walk and Timed Up and Go Test. The fourth RCT [100] included in the systematic Cochrane review [92], investigated the effects on MSS, fatigue, cognitive impairment and mood of two different aerobic physical activities: sports climbing and yoga. This trial included 20 participants with relapsing remitting or progressive MS, which were randomly allocated to a 10-week intervention period. No significant improvements in MSS were found from either intervention (measured using MAS). It is however worth noting, that in the sports climbing group, there was a significant reduction in EDSS pyramidal functions score, while in the yoga group there was a significant increase in selective attention performance.

Despite the lack of robust evidence from RCTs in MSS, there is a strong expert consensus that, in clinical practice, rehabilitation programs aiming to improve passive and active motor function should be recommended [51, 96]. However, caution is warranted to avoid unwanted increase in muscle tone. Sustained passive muscle stretching with extended positions of the extremities may improve the passive range of motion [51, 101]. In addition, there is promising evidence that the damage-oriented training ("Impairment-Oriented Training"), which includes the systematic repetitive training of a paretic limb, as well as modified "Constraint-Induced Movement Therapy" protocols, may have beneficial effects on motor function while attenuating spasticity in paretic extremities [51, 102, 103]. Similarly, device-assisted physiotherapy should be considered in passive and passive-active therapy protocols [51]. Finally, it should be stressed that besides physical therapy, occupational therapy, logotherapy (speech therapy), nutrition monitoring to prevent muscle wasting and osteoporosis, as well as psychological support should all be included in multimodal programs tailored for MSS patients (Table 5).

7b. *Casting, splints and orthotic devices*

Splints, casts and orthotic devices can be classified as aids used in extremities with spastic paralysis for tone and posture regulation as well as for contracture prophylaxis. They may be used alone or in combination with other MSS therapies [51]. The term "casting" or "serial casting" refers to the sequential use of several casts for the treatment of a spastic contracture (with restricted passive range of motion: pROM). A therapeutic improvement of the pROM in the affected extremity is achieved by means of individualized casts made serially in specific joint angles. Previous studies have shown that splint/casting treatment is ineffective for the prevention of spasticity and contractures [104].

However, for cases with chronic spasticity, positive effects have been described by the use of various types of splints at the elbow, wrist [105, 106], ankle and foot [107]. Interestingly, a positive effect has also been reported with combined use of casting and BoNT therapy in patients with spastic contractures [108]. Moreover, with respect to orthotic devices, ankle-foot orthoses (AFO) are frequently used in patients with MSS. AFO by covering the foot and ankle area, can either be completely rigid to immobilize

the ankle or may encourage movement in certain directions. The dynamic AFO helps in controlling foot drop, facilitating normal posture in an upright position, improving the gait pattern, and preventing falls. Although the criteria according to which casting, splints and orthotics should be used in clinical practice are not sufficiently addressed or described in clinical studies, there is expert consensus that these aids may be considered especially for patients with severe forms of MSS with concomitant contractures. The serial application of plaster casts (closed casting) may also be considered, for example in the ankle, to facilitate posture correction [109].

Consequently, aided positioning in pain-free stretching position is advisable for spastic muscles, whereas for severe forms of MSS with incipient spastic contractures (i.e., in the ankle or in the finger flexors) the serial application of closed casts and plaster casts can be recommended, alone or in conjunction with pharmacological therapies (including BoNT therapy) [51].

7c. *Repetitive magnetic stimulation and transcranial direct current stimulation*

Repetitive transcranial magnetic stimulation (rTMS) comprises a non-invasive brain stimulation technique that is painless and well-tolerated, and can induce changes in cortical excitability both at the site of stimulation and at remote sites, while resulting in either facilitation or inhibition of neuronal networks depending on the frequency and pattern of pulses [110, 111]. The effects of rTMS are mediated by induction of short-term and long-term synaptic plasticity. Therapeutic protocols of rTMS are currently implemented in several neurological disorders [111]. Intermittent theta burst stimulation (iTBS) is a recently developed high-frequency and short-duration rTMS protocol, which induces long-lasting effects while being well-tolerated in clinical practice [112]. The use of rTMS in MSS treatment has been systematically reviewed in the literature by independent research groups and expert panels [40, 113]. In a recent systematic review assessing MSS interventions using the GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) [40, 114], 5 rTMS trials were evaluated [115-119], 3 of which were double-blind sham-controlled randomized controlled trials [116, 118, 119] and 2 were pseudo-randomized sham-controlled trials [115, 117]. With respect to MSS outcomes measured with MAS, a treatment effect was observed with real but not sham stimulation in 3 out of 4 trials [115, 117, 118], whilst one trial [116] found improvement in MAS in both groups, without significant between-group differences. In the fifth trial [119], a significant benefit of real versus sham stimulation was noted on MSS outcome measures, as well as on QoL outcomes. Due to inherent methodological limitations of these trials, a weak recommendation in favor of rTMS for the treatment of MSS was formulated based on the previous data [40]. Similar recommendations have been issued in the recently published consensus paper of evidence-based guidelines for the therapeutic use of rTMS in MSS, suggesting a probable benefit of rTMS (iTBS protocols) applied over the primary motor cortex (level B evidence) [113]. Moreover, there are indications that in patients with incomplete paraplegia, high-frequency rTMS (or iTBS) of the parasagittal motor cortex (leg representation area) may improve leg spasticity, especially when combined with gait training [120, 121].

Peripheral repetitive magnetic stimulation (prMS), applied directly over the nerve roots (paraspinal stimulation targeting the spastic muscles in the upper or lower extremities), may also be used for spasticity treatment. Whether a clinically-relevant treatment effect can be achieved by prMS is still unclear from the available observational studies [122]. A Cochrane Review reported that there is currently inadequate evidence to permit any conclusions regarding the routine use of rPMS in patients with spasticity after stroke [123], while the potential utility of prMS in MSS treatment has not been systematically studied. Nonetheless, expert recommendations suggest that prMS has an excellent safety profile and may be considered especially for patients with persistent MSS despite the combined use of other pharmacological and non-pharmacological interventions, provided that the practitioner is competent in implementing this technique [51].

With respect to transcranial direct current stimulation (TDCS) there are currently insufficient data to recommend its use in MSS treatment. A large number of published TDCS studies suffer from major methodological limitations, precluding any inferences regarding the potential benefits of TDCS in MSS treatment. In particular, 13 TDCS studies were assessed in a recent systematic review using GRADE analysis [40]; a total of 12 were excluded for a variety of methodological reasons, including outcomes unrelated to MSS (n = 2), non-comparable drug/interventions (n = 6), unspecified study type (n = 3), review (n = 1). Only one study was finally included in the GRADE analysis [124], a single-center, randomized, double-blind, sham-controlled trial with MAS as the primary end-point. This trial failed to detect any benefit of TDCS [124].

7d. *Transcutaneous electrical nerve stimulation (TENS)*

Transcutaneous electrical nerve stimulation (TENS) of the antagonists of spastic muscles has been suggested to reduce spasticity and to enhance the pas-

sively restricted range of motion (pROM) of affected muscles [125]. In addition, application of TENS on the muscle-tendon junction of spastic gastrocnemius can improve functional gait parameters [126]. A systematic review of RCTs using TENS as spasticity treatment, comprising 207 post-stroke patients, 84 MS patients, and 39 patients with paraplegia, concluded that, although TENS may be useful in clinical practice because of its low cost, ease of use, and absence of adverse reactions, the high variability of therapeutic clinical study protocols precludes any robust conclusions regarding TENS efficacy [127]. Similar results were obtained from a systematic review using GRADE assessment, which concluded that there is currently insufficient evidence to support the use of TENS for MSS treatment [40, 128]. Notably, in clinical practice, the effects of TENS on spasticity appear to be stronger when TENS is combined with active therapy (e.g., exercise and task-related training) [129].

Functional electrical stimulation (FES) is a technique that combines electrical stimulation with intended or partially self-performed activities (e.g. grasping and manipulating or walking) and has been suggested to improve spasticity, motor and walking ability [130]. Notably, FES devices generate low level electrical impulses that stimulate nerves to generate muscle contractions and have the ability to target specific muscles at a specific time. Furthermore, electroacupuncture has been suggested to improve motor performance, spasticity and activities of daily living [131]. Currently, there are no robust data from large RCTs on FES or electroacupuncture to support their use in MSS.Their potential utility should be individually assessed in selected patients [51].

7e. *Other non-pharmacological interventions*

Currently, there is insufficient evidence to recommend the use of thermal stimuli for MSS treatment [51]. A study using alternating daily heating and cooling in hemiplegic upper extremities failed to document any lasting effects on muscle tone [132]. Similarly, as already mentioned in previous sections, there is no evidence to support the use of whole body vibration (WBV) for MSS treatment [133]. Nonetheless, WBV may be associated with reductions of muscle spasms and pain in MS patients [99], and has been suggested that it may alleviate spasticity for short periods of time in patients with paraplegia [134]. Finally, there are insufficient data to date in support of the use of extracorporeal shock wave therapy (ESTW) in MSS [135]. Nonetheless, as ongoing research on the aforementioned modalities will expectedly facilitate the optimization of therapeutic protocols, the utility of these therapeutic interventions should be assessed in the future in the context of well-designed RCTs in MSS patients.

8. Pharmacological therapies for MSS

The selection of pharmacological therapies for MSS should take into account the distribution of MSS (focal, multifocal, segmental, generalized), the type of MSS (continuous or paroxysmal), MSS complications and MSS-related symptoms. Individualized risk-benefit assessment is recommended, as most pharmacotherapies have distinct adverse-effect profiles that should be evaluated when deciding to initiate or modify MSS treatment. Particular caution is warranted when choosing pharmacological therapies for patients with MSS and predominantly brain-localized MS lesions. In contrast to patients with spinal cord lesions, MS patients with high brain lesion-load typically have reduced tolerance to central side effects of oral antispastic treatments [51]. The most frequent pharmacological therapies used for MSS include centrally-acting oral antispastics, such as baclofen, tizanidine, benzodiazepines, gabapentin and nabiximols; the peripherally-acting oral antispastic dantrolene; intrathecally applied antispastics, including baclofen; as well as intramuscular treatments with various BoNT regimens. In the following sections, an overview of the pharmacological therapies for MSS will be presented, along with recommendations for their use in clinical practice.

8a. *Oral agents for MSS treatment*

The oral agents most frequently used in clinical practice to treat MSS are baclofen (gamma-amino-butyric acid [GABA]-B agonist), tizanidine (central alpha-2 agonist), benzodiazepines (GABA-A agonists), gabapentin (GABA analogue), and dantrolene (muscle relaxant inhibiting the release of calcium ions in the muscle) [93, 136]. Of those, dantrolene is the only antispasticity treatment acting primarily on muscles, decreasing the excitation-coupling reaction involved in muscle contraction through inhibition of the calcium release from the sarcoplasmic reticulum [93]. In addition, an oromucosal spray (Sativex®) consisting of 2 cannabis derivatives (tetrahydrocannabinol [THC] and cannabidiol [CBD] in a ratio of 50% THC to 50% CBD) has been recently approved for the treatment of spastically increased muscle tone in MS, and is particularly effective against painful spasms [51, 137-140] (Table 6). This oromucosal spray, acts as a partial agonist at cannabinoid receptors exerting both central and peripheral effects, which are mediated by inhibitory neurotransmitters that cause muscle relaxation [141].

Independent studies using MSS assessment scales (e.g. AS, MAS), have provided preliminary evidence supporting the beneficial effects of oral antispastics on MSS; however, MSS reduction does not always translate into clear functional benefits or QoL improvement (i.e., improvement in daily activities) [4, 142]. In fact, discrepancies between spasticity

Table 6. Overview of pharmacological agents used for MS-related spasticity (MSS)

Active ingredient	Dosing	Mechanism of action	Side effects
Baclofen	10-100 mg/d	GABA-B agonist	Fatigue, dizziness, muscle weakness, falls, dependency, epileptic seizures, risk for misuse
Tizanidine	6-36 mg/d	Alpha-2 adrenergic receptor agonist	Fatigue, dizziness, hypotension and bradycardia, constipation, xerostomia, liver dysfunction
Gabapentin	300-3600 mg/d	GABA- agonist, voltage-gated calcium channels	Fatigue, dizziness, headache, hypotension
Diazepam	5-30 mg/d	GABA-A agonist	Fatigue, dizziness, ataxia, hypotension, muscle weakness with falls, constipation, bladder dysfunction, dependency especially in night spasticity
9-delta-THC / cannabidiol	32.4/30 mg/d & 10.8/10 mg/d respectively	CB1/2 receptor agonist	Fatigue, dizziness, weakness, nausea, depression, psychotropic properties
Intramuscular botulinum toxin	In Table 7	Inhibition the acetylcholine release	Local irritation, bleeding, muscle weakness, incontinence
Intrathecal baclofen	25-1200 μg/d	GABA-B agonist	Bladder and sexual dysfunction, nausea, vomiting, hypotension, respiratory failure, epileptic seizures

Abbreviations: GABA: Gamma aminobutyric acid, THC: Tetrahydrocannabinol, CB1/2 receptor: Cannabinoid receptors subtypes 1/2.

reduction and functional outcomes have been reported in patients suffering from spasticity following initiation of antispastic treatments. For example, a recent meta-analysis of 7 RCTs on systemically-acting antispastic drugs versus placebo, comprising 403 patients with spasticity, failed to detect between-group differences in functional outcome measures [143). Conversely, a significant risk of adverse events per participant was observed in the treatment compared to the placebo group (risk ratio (RR): 1.65, 95% CI 1.12 to 2.42) [143). These data indicate that adverse effects of systemically acting antispastic therapies may hamper the potential benefits of these drugs on functional improvement.

Centrally-acting oral pharmacotherapies exert their antispastic effects by decreasing the excitability of spinal interneurons and motor neurons [51]. Consequently, the limitations of oral MSS treatments are associated with adverse effects on mobility, which are typically dose-dependent, and most frequently involve a decrease in muscle strength [6, 57, 144, 145]. In addition and especially in patients with significant motor impairments, antispastic drugs may significantly affect gait and reduce ambulation [51]. Conversely, immobile patients (e.g., patients with paraplegia or generalized spasticity) are most likely to benefit from oral antispastic therapies, which aim to reduce pain and muscle spasms, while facilitating active-passive mobilization and nursing [6, 40, 51].

Sedation and neuropsychiatric side effects, including depression and cognitive disorders, represent additional side effects of oral antispastic drugs [146, 147]. The clinical indications for MSS treatment, as well as the selection of antispastic agents should be critically assessed on an individual patient basis. A gradual dose titration of antispastic medication is recommended. In order to optimize the tolerability and efficacy of oral antispastic drug treatments it is important to develop individualized dosage regimens. For instance, if a patient has difficulties in getting out of bed, the drugs should be preferably administered after arousal, whereas in patients with predominant nocturnal muscle spasms, increasing night-time doses can be useful [93]. Further aspects need to be considered for a tailored antispastic treatment. For example, as previously noted, MS patients with significant brain lesion-load may exhibit more frequently adverse effects related to sedation compared to those with spinal cord lesions [51]. Thus, these patients should be closely monitored for adverse effects of centrally-acting antispastic drugs, while alternative pharmacological therapies (such as BoNT) or the peripherally-acting antispastic dantrolene may be indicated in selected patients [51].

The most frequent side-effects and recommended dosages of oral antispastic drugs have been summarized in **Table 6**. Briefly, among the centrally-acting oral antispastics, baclofen has predominantly seda-

tive and strength-reducing properties. Typical side effects of tizanidine include xerostomia and drowsiness, while combination of tizanidine with antihypertensive drugs may cause significant decreases in blood pressure [148, 149]. Moreover, tizanidine has been linked to increased risk of hepatic dysfunction; thus, it is recommended that liver function monitoring is performed monthly for the first 6 months of treatment and periodically thereafter. Furthermore, predominant sedative effects are typically noted in patients treated with benzodiazepines, gabapentin and nabiximols, while dantrolene has been associated with a substantial risk for hepatotoxicity (0.7-1%; severe hepatitis or liver failure 0.1-0.2%) [150]; thus, strict monitoring of patients undergoing dantrolene treatment is advisable. It should be stressed that adherence to recommendations concerning dosing and monitoring is advisable in accordance with the Summary of Product Characteristics (SPC) of each approved pharmacotherapy. In the following sections, the efficacy of different oral drugs used in MSS will be briefly presented.

8a-1. *Oral baclofen*

Oral baclofen is a structural GABA-analogue, which binds to pre- and postsynaptic GABA receptors, decreasing activity in motor neurons and interneurons [136]. In clinical practice, symptom control is typically achieved with doses up to 60 mg, with a maximum daily dose of 100 mg. The effects of oral baclofen have been systematically examined in a recent systematic review of RCTs and observational studies in patients with MSS [136]. In this systematic review, evidence on MSS treatments was assessed using prespecified levels of certainty (class I, II, III and IV) [151]. The use of oral baclofen for MSS was examined in 9 randomized [152-160] and one non-randomized [161] controlled clinical trials. Six out of 7 placebo-controlled trials [152, 154, 156, 159-161] found a significant improvement in MSS in patients treated with oral baclofen compared to placebo, while one identified study, with a lower sample size, found no between-group differences [157] (class II/III evidence). In addition, baclofen was found to significantly improve muscle spasms and clonus [154, 159] (class III evidence). In 3 studies comparing baclofen with diazepam, no significant between-group differences were detected using the AS or other MSS scales [153, 155, 158]. Similarly, no differences were detected with respect to the frequency of reported muscle spasms between the two drugs [155, 158] (class III evidence). Additionally, high versus low doses of baclofen (30 or 60 mg) and diazepam (15 or 30 mg) were assessed in one trial [153]. Even though both doses of both drugs showed a significant change in the AS score pre- and post-treatment, there was a marked improvement in patients who were able to tolerate higher doses (class III evidence). In the majority of analyzed trials, baclofen showed an improvement in spasticity compared to placebo, with no differences compared to diazepam. However, side effects, including weakness, drowsiness, paresthesia and xerostomia were common (10%-75%) limiting the maximum tolerated dose, but were fewer in patients treated with oral baclofen compared to diazepam [162].

In line with the previous findings, another recently published systematic review and consensus paper on the use of pharmacological therapies for MSS [40], included 4 double-blind, placebo-controlled studies, analyzing the effects of oral baclofen therapy on AS scores and spasticity NRS, in a GRADE analysis [152, 156, 157, 161]. The authors concluded that the quality of evidence was very low; there was however a consensus for a weak recommendation for the use of oral baclofen for MSS treatment [40].

8a-2. *Tizanidine*

Tizanidine is a short-acting muscle relaxant which acts via stimulation of the central alpha-2-adrenergic receptors, and leads to attenuated release of excitatory neurotransmitters at spinal and supraspinal levels [136]. Tizanidine is typically started at a dose of 2 mg daily, and can be increased up to a maximum dose of 36 mg daily with an average effective dose between 12 and 24 mg [107]. In a systematic review of pharmacological therapies for MSS, 13 trials that examined tizanidine for MSS treatment were identified: two assessing tizanidine in a single dose compared to placebo [42, 163] and 11 assessing the medium-term use of the drug (5-15 weeks) compared to placebo [164-167], diazepam [168] or baclofen [169-174]. A detailed analysis of the results of these trials can be found in the systematic review by Otero-Romero et al. [136]. In summary, this systematic review showed that tizanidine was superior in reducing MSS in the short and medium-term compared to placebo, while being equally effective to diazepam or baclofen. Among the reported side effects of tizanidine, which were mostly related to its alpha-2-adrenergic activity, drowsiness and xerostomia were the most prevalent, while a dose-dependent effect was reported. Moreover, decreases in heart rate and blood pressure were observed, and tizanidine was also related to transient increases in the levels of transaminases, which returned to normal levels after discontinuation of treatment [175].

In accordance with the previous findings, a recent meta-analysis assessing the effects of tizanidine on MSS compared to placebo, included 6 studies in a GRADE analysis [40], 5 double-blind, placebo-controlled trials [42, 167, 168, 176, 177], and one double-blind, double-dummy, two-way crossover,

placebo-controlled RCT [178]. The authors concluded that there were various methodological limitations in the identified studies. Therefore, this study group concluded that there was consensus for a weak recommendation for the use of tizanidine in MSS [40].

*8a-3. **Benzodiazepines***

Given the side-effect profile of benzodiazepines, including their addiction potential and the associated increased risk for misuse and abuse, these drugs should be considered as second-line treatments in MSS [179]. Diazepam is known to enhance the effect of the neurotransmitter GABA and contributes to muscle relaxation via suppression of neuronal activity in the reticular formation [136]. The maximum recommended dose is 30 mg/day, with an average dose of 15 mg. In a systematic review of clinical trials on pharmacological treatments for MSS [114], diazepam was shown to have a comparable efficacy to baclofen with respect to MSS, although more sedation was observed with diazepam (class III evidence) [153, 155, 158]. In comparison to dantrolene, tizanidine or ketazolam, a similar reduction of MSS was observed with diazepam (class II/III evidence) [168, 180-182].

In another systematic review, 3 clinical studies were included in a GRADE analysis [153, 155, 168], two of which compared diazepam to baclofen [153, 155], and the third was a RCT comparing diazepam to tizanidine [168]. The authors reported that diazepam was associated with significant reductions in muscle tone; however, there were no significant differences compared to the efficacy of tizanidine and oral baclofen. Accordingly and based on the reported effects of oral diazepam, which were not superior to the comparator (oral baclofen or tizanidine) and the limited tolerability of the drug, the authors agreed on a weak recommendation for the utilization of benzodiazepines for MSS treatment [40].

8a-4.*Gabapentin*

Gabapentin represents a structural analogue of GABA, which exerts GABAergic activity by binding to receptors in the neocortex and hippocampus [136]. The normal starting dose is 300 mg/day, which can be escalated up to a maximum daily dose of 3600 mg. A systematic review of studies assessing the effects of gabapentin on MSS, included two randomized, placebo-controlled short-duration crossover RCTs [183, 184].

The higher dose study [183] (up to 900 mg gabapentin per os 3 times daily over a 6-day period) found a significant reduction in all physician-assessed measures and subject-reported MSS outcomes. The lower dose study [184] (400 mg gabapentin per os three times daily for 48 hours) reported also a reduction in the modified AS scores, but no effect on clonus, reflexes or response to noxious stimuli (class II evidence). The main adverse effects included drowsiness, somnolence and dizziness, albeit treatment was generally well tolerated, with no serious side effects reported [183, 184].

The same RCTs were included in a systematic review using GRADE analysis [40], prompting the authors to agree on a weak recommendation for using gabapentin to reduce spasticity in MS patients.

8a-5. *Dantrolene*

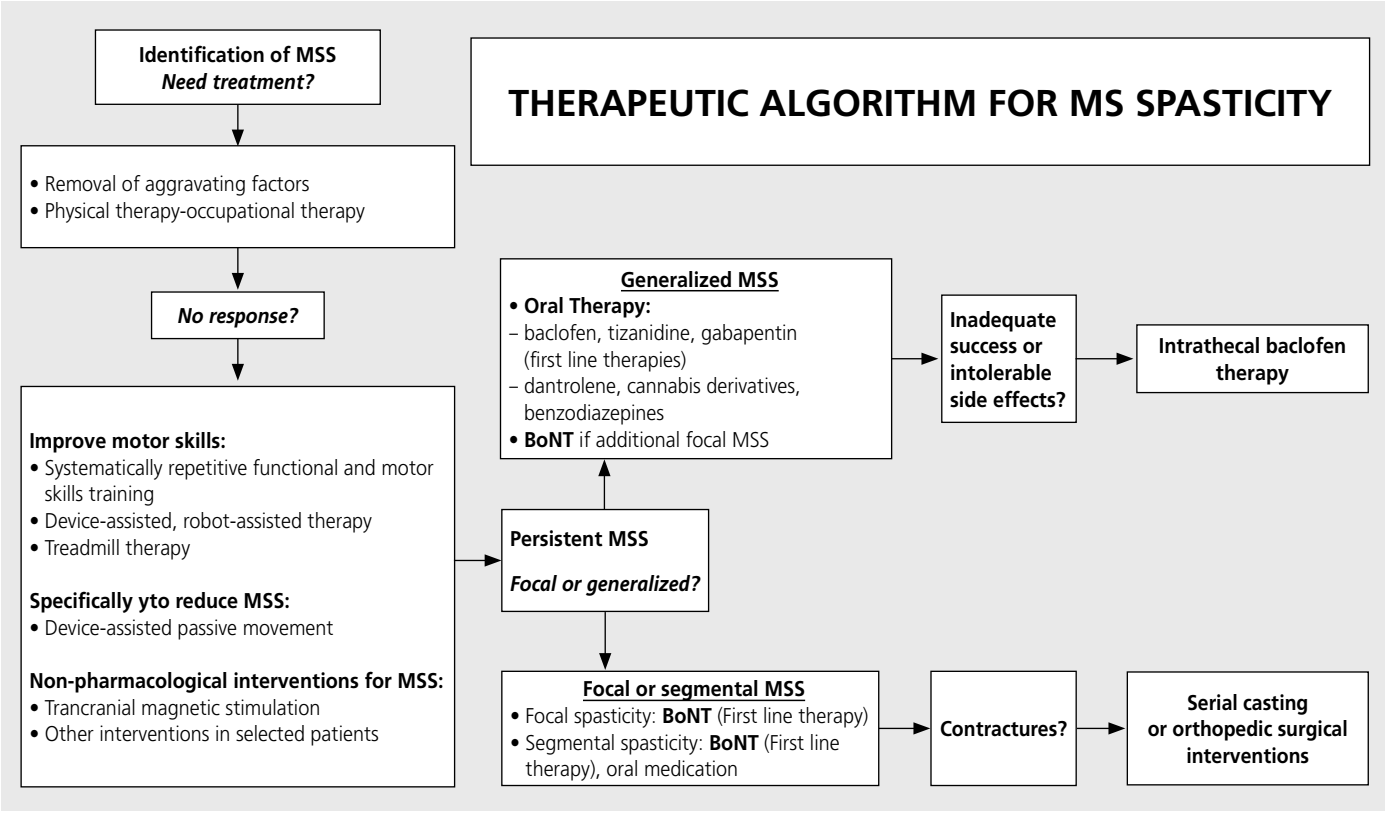
Dantrolene exerts its effects on the contractile mechanism of skeletal muscle via reduction of calcium release [136]. Treatment is usually started at 25 mg once daily and increased gradually to a maximum of 400 mg divided into four doses. In the previously presented systematic review by Otero-Romero et al. [136], 3 clinical studies assessing dantrolene for MSS were identified: two small studies comparing dantrolene with placebo [185, 186], starting at 50 or 25 mg four times daily, respectively, and titrated to a maximum of 100 mg. A significant reduction in MSS was noted using semi-quantitative scales in 42% of patients on dantrolene and 27% on placebo [186]. In addition, a third trial was included in this systematic review, that compared dantrolene to diazepam [180]. Although both dantrolene and diazepam reduced MSS at low and high doses, this reduction was significantly greater in patients treated with dantrolene at higher doses. The patients reported subjective improvement for two symptom-categories (muscle spasms or cramps and stiffness), while no statistical differences were detected between drugs.

This review concluded that the use of dantrolene is superior to placebo using objective and subjective measures, albeit this conclusion was based on studies with low-quality of evidence [136]. It should be noted that in clinical practice the use of dantrolene is restricted due to the high frequency of side effects, including gastrointestinal symptoms, weakness, fatigue, sedation and dizziness. Moreover, as already discussed in previous sections, the risk of hepatotoxicity is a major limiting factor that necessitates monitoring of liver function prior and during therapy [51, 136, 150]. Taken together, the previous results suggest that the use of dantrolene should be restricted only to patients who show lack of MSS improvement despite treatment with oral pharmacotherapies, including baclofen, tizanidine or gabapentin (Figure 2). Also, since weakness is a frequent side effect of dantrolene, this drug may be reserved for non-ambulatory patients [136].

8a-6. *Nabiximols*

Nabiximols (Sativex®) is an oromucosal spray of cannabis extract containing THC and CBD and is currently the only approved cannabis-based drug for MSS

Figure 2. Therapeutic algorithm for multiple sclerosis spasticity



Abbreviations: MS: multiple sclerosis, MSS: multiple sclerosis-related spasticity, BoNT: botulinum neurotoxin

treatment [136, 187]. Therapy usually starts with a 2-week dose titration phase, up to a maximum daily dose of 12 sprays. Nabiximols has been tested during the past years against placebo in MS patients with a variety of symptoms (spasticity, spasms, tremor, bladder problems, or pain). A systematic review and meta-analysis including 3 randomized, placebo-controlled, double-blind parallel group studies in 666 patients with MSS, demonstrated that nabiximols is well tolerated and reduces MSS significantly compared to placebo [138].

Many RCTs have corroborated to date the superiority of nabiximols compared to placebo in reducing MSS, while nabiximols has also been associated with improved spasm frequency, reduced sleep disruption and improved functional outcomes [188]. In the systematic review by Otero-Romero et al. [136], nabiximols was found to have a positive effect on MSS without serious adverse effects, when used as an add-on therapy. Nevertheless, an increased incidence of non-serious adverse events was noted, with dizziness being the most frequently reported symptom [189].

In another systematic review, 13 studies on nabiximols for MSS treatment were included in a GRADE analysis [40], in which different outcomes including AS, MAS, NRS, MSSS-99 and spasticity VAS were evaluated. The expert panel of this consensus paper agreed that evidence exists to recommend cannabinoids, and particularly oromucosal spray of nabiximols, for the treatment of MSS and based on the analyzed evidence, the strength of recommendation was strong.

Taken together, the previous evidence supports the use of nabiximols for MSS treatment, especially in patients with a suboptimal therapeutic response or poor tolerance of other pharmacotherapies [136]. It should be stressed, however, that close monitoring of the therapeutic response is warranted, as approximately only half of treated patients respond to nabixomols treatment, and discontinuation should be considered in case of absence of net clinical benefit or if significant side effects are present [125]. It should be noted that a position paper issued by the National Institute for Health and Care Excellence (NICE) [190]supported the efficacy and safety of nabiximols in MSS. Nevertheless, a final recommendation against the use of nabiximols in clinical practice was made due to unmet cost-efficacy requirements. Thus, the possibility of reimbursement should also be considered when prescribing nabiximols in clinical practice.

8a-7. *Summary of recommendations on oral pharmacotherapies*

Taken together, the previous evidence on oral pharmacotherapies for MSS indicates that there are limited data from RCTs to guide the choice of antispastic treatments in MSS, while most oral antispastic drugs have a narrow therapeutic range requiring cautious titration and close patient monitoring [191]. In clinical practice, there is consensus that in patients who experience non-focal MSS, with significant impact on daily life (i.e., interference with activities of daily living or MSS-related pain), oral baclofen should be considered as one of the first treatment options [51, 136]. Given the potential risk for dose-dependent side effects, baclofen therapy should be initiated at low dose (5-10 mg daily) and gradually titrated upwards to a maximum of 100 mg/day. We recommend the use of tizanidine as an alternative to baclofen, given the similarities in efficacy between the two drugs. To minimize dose-dependent side effects of tizanidine, initiation of treatment with 2 mg daily, with slow titration to a maximum of 36 mg is recommended. Crucially, monitoring of liver function should be performed monthly for the first 6 months of treatment and periodically thereafter. Gabapentin comprises another alternative to baclofen and tizanidine, with acceptable safety profile; however, there are scarce data regarding its efficacy in MSS, while head to head comparisons between gabapentin and other pharmacological therapies for MSS are missing. Gabapentin may be particularly considered for patients with MSS and neuropathic pain, or fluctuating MSS with paroxysmal components of spastic dystonia. Given the increased risk of side effects associated with the use of benzodiazepines, including the increased risk for addiction and misuse, diazepam should be reserved for patients that experience severe MSS and have failed alternative treatment options. Dantrolene and nabiximols may be indicated for selected patients who experience MSS despite combined use of other non-pharmacological and pharmacological treatments. Finally, a stepwise approach to MSS therapy is preferable, favoring monotherapy over drug combinations, although combination of drugs may be clinically useful, but requires careful titration to establish a both effective and tolerable treatment regimen. A summary of the presented recommendations is provided in Figure 2.

8b. *Intrathecal therapies*

8b-1. *Intrathecal baclofen*

Baclofen does not effectively cross the blood-brain barrier when administered orally; thus, intrathecal baclofen (ITB) achieves much higher concentrations in the CSF [192]. A surgically implanted pump with reservoir achieves a 4 times higher concentration of the drug at the 1% of oral dosage [136]. In clinical practice, pump implantation may be considered only after testing responsiveness and determining optimal individual doses. Typically, treatment is started at a dose of 25 μg/day, increasing over the first 6 months up to an average of 400 to 500 μg daily.

A systematic review assessing RCTs on ITB for MSS, identified 3 RCTs [193-195] that examined the effect of ITB infused by programmable infusion pumps, after having asserted responsiveness to treatment. A long-term multicenter placebo-controlled trial comprising 22 patients who underwent ITB [194], found significant improvements in the AS scores in the active treatment group, as well as significant improvements in the spasms score and the self-reported pain score (class I evidence). These results were corroborated in a larger multicenter trial [193] (class III evidence), and in a short-term placebo-controlled crossover trial [195] (class II evidence). Similar results were also obtained by an independent systematic review [40] that based on the results of 2 RCTs assessing the effects of ITS on AS scores [194, 195], concluded that, despite the low quality of identified studies, there was strong consensus for the use of ITS for MSS treatment.

ITB can be an effective treatment alternative to oral medications in patients who have severe MSS and a suboptimal response to oral medications, or poor tolerance due to side effects of oral pharmacotherapies. Side effects caused by the drug itself are uncommon [136], with the most common being drowsiness, dizziness, blurred vision and slurred speech. Technical complications are mainly related to the surgical procedure, while pump and catheter dysfunction have also been reported in clinical studies [193, 195]. ITB may be considered especially in patients with lower limb spasticity, while the effects of ITB should be assessed prior to implantation, with an external pump that infuses baclofen and allows assessment for responsiveness, including the effects on walking ability [2]. Recently, several studies have argued that ITB therapy may be underutilized in the MS population due to to underestimation of the impact of MSS on QoL and to concerns about the cost and safety of ITB therapy [2]. Delivery of ITB therapy requires expertly trained staff and proper facilities for pump management; there is strong expert consensus that ITB should be considered in patients with persisting MSS despite conventional treatments [191], while a careful selection of patients and establishment of realistic and mutually agreed treatment goals are recommended [136]. The efficacy of ITB in functional status improvement and pain reduction in patients with severe MSS or spinal cord injury has been also shown in a Greek cohort [67].

8b-2. *Intrathecal phenol*

In the systematic review of Otero-Romero et al.

[136], no RCTs evaluating the effect of intrathecal phenol on MSS were identified. Four identified observational studies were reviewed [196-199]. Of those, two studies reported descriptive results in terms of general relief of MSS (class IV evidence) [196, 197]. A cross-sectional observational study compared the effects of initial phenol injection (initial group) versus subsequent injections (serial group) in different muscle groups, showing a significant reduction in the AS scores in both groups (class IV evidence) [198]. Finally, in a retrospective observational study comprising 34 MS patients, intrathecal phenol was associated with MSS improvement assessed by a simple rating scale and by attainment of rehabilitation goals (class IV evidence) [199]. Thus, there is insufficient evidence to support the use of phenol intrathecal injections for MSS treatment, while the very low quality of the aforementioned studies precludes any meaningful inferences regarding the potential utility of intrathecal phenol in the MS patient population.

8c. *Botulinum neurotoxin therapy (BoNT)*

BoNT acts by inhibiting acetylcholine release from nerve endings, thereby causing presynaptic neuromuscular block and impeding muscle contraction [200]. The neurotoxin is produced by anaerobic Gram-positive bacteria of the Clostridium genus. Local injection of BoNT in isolated muscles has effects that typically last for several weeks to months, while the blockage of neurotransmitter release by BoNT is irreversible [201]. Neuromuscular function has been shown to recover by sprouting of nerve terminals and formation of new synaptic contacts [201]. So far, BoNTs have been classified into 8 different serotypes denoted with different alphabetical letters (A to H). Among these, serotype A is almost exclusively used for therapeutic purposes, as it provides the most consistent efficacy [202]. In total, 3 type A and one type B botulinum toxins have been approved by the FDA (U.S. Food and Drug Administration) for clinical use. Botulinum toxins type A include onabotulinumtoxin A (Botox®), incobotulinumtoxin A (Xeomin®) and abobotulinumtoxin A (Dysport®). The type B is rimabotulinum toxin (Neurobloc®). The following bioequivalent units between these toxins have been suggested in RCTs: 1 unit of Onabotulinum toxin A = 1 unit of incobotulinum toxin A =3 abobotulinum toxin A units = 40-50 units of rimabotulinum [203]. Nevertheless, there are substantial variations in bioequivalence among different BoNT across different muscles [204].

Upper and lower limb spasticity, regardless of the underlying cause of spasticity, are now FDA-approved indications for BoNTs based on data provided by large multicenter studies, which also included MS patients [205]. Although current SPCs of BoNTs approved in Greece do not include MSS in the indications for BoNT treatment, there is expert consensus that BoNT can be safely and effectively utilized in the treatment of upper and lower limb spasticity in MS, similar with the provided recommendations for BoNT use in the treatment of post-stroke spasticity [40, 51, 136, 206]. According to currently approved SPCs, the BoNT regimens available in Greece for treatment of post-stroke upper and lower limb spasticity include onabotulinumtoxin A (Botox®) and abobotulinumtoxin A (Dysport®) (Table 7). It is worth noting, that recommendations regarding the therapeutic use of BoNT for the management of post-stroke upper and lower limb spasticity have been previously published in a consensus document of the Hellenic Neurological Society, the Hellenic Society of Cerebrovascular Diseases, and Hellenic Society of Physical and Rehabilitation Medicine [207]. In the following sections, the data regarding the therapeutic use of BoNT for MSS treatment will be presented, along with recommendations of an expert panel regarding their implementation in clinical practice for the treatment of upper and lower limb spasticity in MS patients.

A recent systematic review including clinical studies on BoNT for MSS treatment [136], identified a total of 5 studies, 3 of which were excluded from subsequent analysis due to methodological reasons [case-series design [208], MS patients representing less than half of the sample [209], and open-label uncontrolled design [210]. The two available placebo-controlled RCTs studied the commercial preparations Botox® or Dysport® [47, 211]. The first RCT [211], published more than 30 years ago, demonstrated the efficacy of onabotulinumtoxin A (Botox®) in MSS of leg adductors by using a double-blind, placebo-controlled crossover study design. Nine patients, who were either chair-bound or bed-bound with chronically stable MS were included. Adductor brevis, longus, and magnus muscles were injected with 100, 100, and 200 mouse units (MU) of onabotulinumtoxin A, respectively. The study demonstrated that BoNT was associated with a significant reduction in spasticity and a significant improvement in the ease of nursing care, while no adverse effects were reported (class III evidence). In the second RCT [199], 74 patients with definite or probable MS, and disabling MSS affecting the hip adductor muscles of both legs, were randomized to one of 4 groups, to receive abobotulinumtoxin A (Dysport®) (500, 1000 or 1500 Units), or placebo by intramuscular injection in the hip adductor muscles. The study found a significant improvement in the measured distance between the knees during passive movements for the 1500-Unit group compared to placebo, and significant improvements in hygiene for the 1000- and 1500-Unit groups. Pain and spasm frequency improved to a similar extent in all 4 groups, but significant changes in muscle tone

Table 7. Recommendations regarding intramuscular injections of onabotulinumtoxinA and abobotulinumA for MS-related spasticity (MSS)

Muscle group		Botulinum toxin agents			
		Onabotulinum toxin		Abobotulinum toxin	
Clinical Pattern	Muscles	*Range of dose (Units)*	*Max. No of injection sites per muscle*	*Range of dose (Units)*	*Max. No of injection sites per muscle*
Flexed Wrist	Flexor Carpi Radialis	50-75	2	100-200	
	Flexor Carpi Ulnaris	25-50	2	100-150	
Clenched Fist	Flexor Digitorum Superficialis	40-50	2	100-150	
	Flexor Digitorum Profundus	25-60	2	100-200	
	Flexor Pollicis Brevis	10-15	1		
	Flexor Pollicis Longus	25-30	2	100-200	
	Adductor Pollicis Longus	10-12.5	1	25-50	
Flexed fingers	Flexor Digitorum Superficialis	25-60	2	100-200	
	Flexor Digitorum Profundus	25-75	2	100-200	
Flexed elbow	Brachioradialis	25-50	2	100-200	
	Biceps Brachii	10-50	4	200-300	
	Brachialis	50-100	2	100-200	
Pronated forearm	Pronator Quadratus	10-25	1		
	Pronator Teres	45-60	2	100-200	
Thumb in palm	Flexor Pollicis Longus	40-50	2	50-100	
	Adductor Pollicis	10-20	1		
	Flexor Pollicis Brevis	12.5-20	1		
Adducted Shoulder	Pectoralis complex	75-100	4	100-200	
	Latissimus Dorsi	75	4		
Adducted Thigh	Adductor Magnus	75-150	2	100-150	
	Adductor Longus	75-80	2	100-150	
	Adductor Brevis	20-25	2		
	Gracilis	25-40			
	Iliopsoas	25-150			
	Medial Hamstrings	50			
Flexed knee	Medial Hamstrings	125	4		
	Lateral Hamstrings	75	4		
	Gastrocnemius	50-200		100-450	1-3
	Iliopsoas	40-150			
	Gracilis	50			

Table 7. Continuity

Extended knee	Rectus Femoris	80-125	4		
	Vastus Medialis	50	2		
	Vastus Lateralis	50-70	2		
	Vastus Intermedius	35-75			
	Gluteus Maximus	40			
Equinovarus Foot	Tibialis Posterior	100	2	100-250	1-3
	Gastrocnemius	125	4	200-300	
	Soleus	75-100	4	150-200	
	Tibialis Anterior	75			
	Flexor Digitorum Longus	20-75		50-200 50-100	1-2
	Flexor Digitorum Brevis	13-38		50-200	1-2
	Flexor Hallucis Longus	25-38		50-200	1-2
	Extensor Hallucis Longus	13-50			
Plantar Flexed Foot Ankle	Gastrocnemius	125	4	100-300	1-3
	Soleus	75	4	150-200	2-4
	Tibialis Posterior	25-75		100-200	
	Long Toe Flexor	20			
Striatal Toe	Extensor Hallucis Longus	50		50	
	Extensor Hallucis Longus Motor Point	38	2		
	Extensor Digitorum Longus	25-30			
Flexed Toe	Flexor Digitorum Longus	50-80	2	50-200 100-150	1-2
	Flexor Digitorum Brevis	25	1	50-200	1-2
	Flexor Hallucis Longus	40-50	2	50-200 50-100	1-2
	Flexor Hallucis Brevis	13		50-100	1-2

were only observed in the botulinum toxin groups. Time to re-treatment was significantly longer for all treatment doses compared to placebo (class I evidence). Concerning side effects, the frequency of muscle weakness was found to be higher in the 1500-Unit treatment group (36%) compared to the placebo group (6%). The authors concluded that the optimal dose for hip adductor spasticity seems to be 500-1000 Units abobotulinumtoxin A (Dysport®), divided between both legs [199].

Despite the small number of patients and the short duration of the previous RCTs, the observed effects on MSS and the safety profile of BoNT (similar to placebo with the exception of muscle weakness) have prompted independent research groups and expert panels to support the use of BoNT for the treatment of MSS [40, 51, 136]. In another systematic review, 4 controlled trials were included in a GRADE analysis: the two previously presented RCTs [47, 211], and two single-blind randomized trials [97, 212]. Giovanelli et al. [97] conducted a single-blind, pilot RCT over a 12-week study period, including 38 patients with progressive MS and focal spasticity of the upper and lower limbs. The aim of this study was to assess whether combined physiotherapy can improve the response to BoNT. All patients included in this study received onabotulinumtoxinA (Botox®), whereas the treatment group received additional physiotherapy with strengthening and stretch exercises. MSS outcomes were evaluated at baseline, 2, 4, and 12 weeks

post-treatment by the use of MAS and VAS scales. Patients with focal MSS of the upper or lower limb were treated with Botox® 100 U diluted (50 U/mL), which was injected in upper limb muscles affected by MSS as follows: in flexor digitorum superficialis (two sites), flexor carpi radialis (two sites) and flexor carpi ulnaris (two sites). Accordingly, in the lower limb muscles, Botox® 100-300 U diluted (50 U/mL) was injected in the tibialis posterior (one site), gastrocnemius medial and lateral (three sites) and soleus (two sites). A significant decrease in MAS scores was observed in the treatment group at all study time points, while combined treatment was more effective as reflected by the significant decrease in VAS measures. Crucially, this study underscored the role of physiotherapy, which in combination with BoNT, can significantly improve the overall response to BoNT in MS patients. Another single-blind, RCT [212], including 42 patients with secondary progressive MS and knee/ankle MSS, suggested that, besides physiotherapy, segmental muscle vibration may have additive effects to BoNT [onabotulinumtoxinA, Botox® 100-300 U diluted (50 U/mL) in the rectus femoris, gastrocnemius medial and lateral, and soleus muscles] and can effectively reduce MSS while improving fatigue in the medium-term follow-up. Importantly, none of the previous studies reported any adverse events from BoNT in MS patients [97, 212]. Taken together, the previous findings have led the authors of the systematic review to conclude [40] that despite the small sample size from clinical studies - with a total of 134 patients treated with BoNT - the quality of evidence was moderate. Therefore, this panel of experts reached a consensus to recommend the use of BoNT for MSS treatment [40].

It should be noted, that despite the compelling data on the efficacy of BoNT in MSS treatment, there is an ongoing controversy in the literature with respect to the magnitude of response to BoNT therapy in MSS compared to stroke-related spasticity [205]. In a study of 99 patients with spasticity [33 MS, 33 stroke, 33 cerebral palsy (CP)], the investigators found that MSS patients required substantially higher doses of BoNT to achieve a significant clinical response [213]. By contrast, a large prospective registry of 508 patients found no differences with respect to dose and magnitude of response to BoNT between different types of spasticity (stroke, traumatic brain injury, MS, CP) [214]. Individualized titration of BoNT is recommended for MSS treatment, while physicians that utilize BoNT should adhere to the approved/recommended dosages of local authorities' guidelines. Table 7 summarizes the recommended dosages per muscle based on expert consensus and in accordance with the recommendations for post-stroke spasticity [207, 215].

Data from clinical studies indicate that even high BoNT doses (e.g., onabotulinumtoxinA doses of ≥600, abobotulinumtoxinA 500-1000 U) are generally well tolerated, causing mostly transient side-effects (most frequently muscle weakness) without any life-threatening complications [216-218]. It should be noted, however, that the maximum total botulinum toxin dose per session should not exceed 400 Units for onabotulinumtoxin A (with possibility to increase to 600 Units per session depending on treatment response) and 1500 Units for abobotulinumtoxin A.

Based on the results of RCTs and meta-analyses, the American Academy of Neurology has recently updated their guidelines on the use of botulinum toxin for the treatment of patients with spasticity [219]. Accordingly, abobotulinumtoxin A, onabotulinumtoxin A and incobotulinumtoxin A are recommended as first line treatment options for upper-limb spasticity (Level of Evidence A), whereas rimabotulinum B should be considered as an alternative treatment (Level of Evidence B) [219]. With respect to lower-limb spasticity, these guidelines suggest that abobotulinumtoxin A and onabotulinumtoxin A are established as effective and should be offered for spasticity treatment (Level of Evidence A). Notably, there is evidence from a randomised, double-blind, placebo-controlled trial comparing BoNT (onabotulinumtoxinA, Botox®) injected into spastic upper limb muscles with oral tizanidine or placebo, showing that BoNT was superior to tizanidine for improving wrist and finger flexor tone, whereas tizanidine showed no benefit over placebo [220]. Moreover, a high incidence of adverse effects with tizanidine in this RCT limited its dose titration [220]. Based on these findings, the American Academy of Neurology recommends that BoNT (with onabotulinumtoxinA) should be considered as a treatment option before tizanidine for treating adult upper extremity spasticity (Level B) [219]. It should be noted, however, that these guidelines do not differentiate between underlying causes of spasticity, and do not provide specific guidelines for MSS treatment.

Perhaps the most robust evidence so far for the use of BoNT has been provided by a consensus paper of the IAB (Interdisziplinärer Arbeitskreis Bewegungsstörungen) – Interdisciplinary Working Group for Movement Disorders task force [206]. In this position paper, the authors performed a systematic literature search, identifying a total of 55 publications (3 RCTs as cited above, 3 interventional studies, 11 observational studies, 2 case studies, 35 reviews, 1 guideline), all of which unanimously favored the use of BoNT for MSS treatment. The committee concluded that based on the reviewed data, there is no reason to assume that BT is less effective or safe in MSS than in post-stroke spasticity; thus, MS specialists should consider BoNT for MSS treatment. In addition, the committee advocated for expansion of

BoNT indications to include all types of spasticity regardless of its etiology, and stressed that SPCs should be promptly updated and approved by national and international regulatory authorities.

Finally, it should be stressed that BoNT for MSS treatment should be applied by physicians trained in its use. The number of injection sites per muscle dependents on their size, the severity of hypertonia, the degree of muscle weakness, and the response to previous injections. Administration of multiple injections may allow for a more uniform contact with the sites of muscle innervation, particularly in larger muscles. Additionally, in extremities that preserve a certain degree of voluntary movement, BoNT injections in selected muscles may contribute to the development of the appropriate conditions for the upper and lower limb that will enable a patient to participate in specialized rehabilitation programs, using for example guided plasticity techniques. In case of insufficient treatment responses, expert panels recommend: 1) increasing dose at a subsequent session, 2) increasing the number of injected muscles, 3) modifying dilution of the product [221]. In addition, ultrasound, electromyography, and electrical stimulation may all be used for guided and more accurate delivery of BoNT, since guided BoNT clearly outweighs the non-guided delivery in various patient groups, including MS patients [222, 223]. Moreover, adherence to a minimum of 12 weeks intervals between injection sessions is recommended to reduce tolerance and prevent formation of neutralizing antibodies (NAbs) against botulinum toxin [224, 225].

Recommendations regarding the use of BoNT in anticoagulated patients have been previously published in the consensus document of the Hellenic Neurological Society, the Hellenic Society of Cerebrovascular Diseases, and the Hellenic Society of Physical and Rehabilitation Medicine on post-stroke spasticity [207]. Briefly, intramuscular BoNT injections for the treatment of spasticity in anticoagulated patients should not be withheld regardless of the localization of targeted muscles [207, 215, 226, 227]. Moreover, it is suggested using 25G sized or smaller needles when injecting into deep compartment muscles of the lower limbs, and the International Normalized Ratio (INR) value should be ≤3.5. In cases of fluctuating INR values or suspected coagulopathy, a recent INR value should be available (last 2-3 days). For cases on direct oral anticoagulants (DOACs), the same precautions as for patients on warfarin and normal INR range should be taken. No dosage modification of DOACs before treatment is recommended [227].

Besides the utility of BoNT in MSS treatment, another indication of BoNT that merits mention involves the treatment of neurogenic bladder dysfunction in MS patients. Although the treatment of overactive bladder requires endoscopic BoNT injections and should be performed strictly by trained urologists or gynecologists, it is important in the context of the present consensus paper to stress that there is level A of evidence (effectiveness in two or more class I studies) supporting that the injection of onabotulinumtoxin A into the bladder's detrusor muscle improves MS-related neurogenic detrusor overactivity (NDO) and MS-related overactive (OA) bladder symptoms [205]. The FDA has approved the use of onabotulinumtoxinA for the treatment of NDO based on the results of two large multicenter studies [228, 229], which included a total of 691 patients, and demonstrated that BoNT can significantly reduce the frequency of urge urinary incontinence and improve urodynamic parameters in patients with NDO. These results have been recently confirmed by independent meta-analyses, indicating that onabotulinumtoxin A is both effective and safe for treating patients with NDO compared to placebo [230-232]. Thus, neurologists, urologists and physical medicine and rehabilitation physicians should be aware of the safety and efficacy of BoNT in the treatment of OA, and refer accordingly MS patients suffering from OA symptoms to allied medical specialties for clinical assessment.

Finally, there are emerging data mostly, based on retrospective class IV studies, demonstrating a potential efficacy of BoNTs in other MS symptoms, including focal myokymia, spastic dysphagia, and double vision due to internuclear ophthalmoplegia [205, 233]. Safarpour et al. have recently reviewed the literature, presenting single observational studies with promising results for the previous conditions [179], whilst they concluded that there is no data to support the use of BoNT for MS-related trigeminal neuralgia and sialorrhea. Even though some small observational studies have provided encouraging results, there is no evidence to date to support the utility of BoNT from large, well-designed RCTs for any of the previous indications. Therefore, no evidence-based recommendations can be formulated for the use of BoNT in MS patients with such symptoms.

9. Conclusions

The present consensus paper of the Hellenic Neurological Society, the Hellenic Academy of Neuroimmunology and the Hellenic Society of Physical and Rehabilitation Medicine provided a summary of the current evidence on pharmacological and non-pharmacological MSS treatments. This document underscores the importance of engaging interdisciplinary groups in MSS management and aims to raise awareness among clinicians for the early recognition and treatment of MSS. Proposed practical algorithms for the diagnostic approach and therapeutic management of MSS have been provided in Figure 1 and Figure 2, respectively.

The main steps of these algorithms are summarized below:

- All MS patients with upper or lower limb paresis/paralysis should be clinically evaluated for the possible presence of MSS using both clinically standardized (AS scale, MAS, Tardieu, or REPAS scale) and functional scales that incorporate patient-relevant symptoms and QoL measures. In addition, the implementation of combined scales is advisable for patient follow-up and monitoring of responsiveness to MSS therapies.
- The initial assessment of MSS should entail thorough assessment of different functional domains (including use of MSFC and EDSS scales), but also of different organ systems to identify possible complications of MSS, including bladder/bowel dysfunction, dysphagia, contractures and limb deformities, as well as pressure sores.
- Before initiation of MSS treatments it is important to assess potential risk factors, including immobility, pain, noxious stimuli, emotional tension, infections, thromboses and fractures, along with potential adverse effects of concomitant treatments; moreover, regular assessment of DMTs is warranted to ensure that disease activity does not contribute to MSS aggravation.
- Establishment of treatment goals should be decided jointly with the patients and their caregivers, considering the patient's daily activities and functional impairment due to MSS.
- In patients with motor deficits and MSS, rehabilitation sessions (including, physical and occupational therapy) are of fundamental importance for the preservation of mobility and functional independence.
- With respect to non-pharmacological approaches, physical activity programs can be used in combination with other interventions against MSS (pharmacological or non-pharmacological). Among non-pharmacological interventions, the use of intermittent/repetitive magnetic stimulation (iTBS/rTMS) with or without adjuvant exercise therapy has the highest level of evidence for improving MSS. Conversely, the use of TDCS, TENS, sports climbing and vibration therapy is not sufficiently supported by evidence from RCTs; however, their implementation in clinical practice, given their good safety profile, may be considered on an individual patient basis.
- Similarly, other non-pharmacological therapies, including hydrotherapy, cryotherapy, thermotherapy, neurodevelopmental inhibitory techniques orthoses/splints and robotic rehabilitation should be performed only in experienced therapeutic centers, as appropriate, and ideally within the settings of clinical trials and as adjunctive to other first-line spasticity treatments.
- With respect to pharmacological therapies, due to the narrow therapeutic range of oral antispastics, a careful titration of dosing is recommended. First-line treatments include oral baclofen and tizanidine, while gabapentin, diazepam, nabiximols and dantrolene may be considered in selected patients under close monitoring for potential side-effects. In addition, intrathecal baclofen pumps may be indicated especially for patients with serious side-effects from oral pharmacotherapies and generalized MSS, whereas phenol pumps have no indication for MSS treatment.
- Intramuscular BoNT injections should be considered in MS patients with upper and/or lower limb spasticity, on the condition that BoNT treatment is delivered by appropriately trained and experienced physicians. The recommendation of BoNT injections appears to have higher level of evidence compared to oral pharmacotherapies for the treatment of focal, multifocal and segmental spasticity.
- Importantly, BoNT treatment should be combined with rehabilitation sessions, as well as with orthoses/splints/casts, electrical nerve stimulation or vibration therapy, as appropriate. The simultaneous use of other techniques, like robotic technology, depends on the experience of each therapeutic center, and is recommended as appropriate, ideally within the settings of clinical trials.
- We recommend adherence to the approved BoNTs dosages according to the respective SPCs. Since MSS has not been included into currently approved BoNT indications, we recommend that muscles/BoNT dosing schemes should be aligned with those approved for post-stroke spasticity. Currently, the approved botulinumtoxin A regimens for both upper and lower limp post-stroke spasticity management in Greece are onabotulinumtoxin A and abobotulinumtoxin A.
- The maximum total botulinum toxin dose per session should not exceed 400 Units for onabotulinumtoxin A (with possibility to increase to 600 Units per session depending on treatment response) and 1500 Units for abobotulinumtoxin A. Ultrasound-guided or electromyography-guided injections are recommended; the needle size should be preferably ≥27G. Anticoagulant treatment is not a contraindication for BoNT injections.
- Finally, BoNT may be indicated for patients with neurogenic bladder dysfunction, and treating physicians should refer early MS patients to allied specialties for consultation and treatment assessment.

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