Journal of Clinical Neuroscience 39 (2017) 16–27

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

Breakthroughs in the spasticity management: Are non-pharmacological treatments the future?

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ARTICLE INFO

Article history:
Received 2 December 2016
Accepted 12 February 2017

Keywords:
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation
Stroke
Multiple sclerosis
Spinal cord injury

ABSTRACT

The present paper aims at providing an objective narrative review of the existing non-pharmacological treatments for spasticity. Whereas pharmacologic and conventional physiotherapy approaches result well effective in managing spasticity due to stroke, multiple sclerosis, traumatic brain injury, cerebral palsy and incomplete spinal cord injury, the real usefulness of the non-pharmacological ones is still debated. We performed a narrative literature review of the contribution of non-pharmacological treatments to spasticity management, focusing on the role of non-invasive neurostimulation protocols (NINM). Spasticity therapeutic options available to the physicians include various pharmacological and non-pharmacological approaches (including NINM and vibration therapy), aimed at achieving functional goals for patients and their caregivers. A successful treatment of spasticity depends on a clear comprehension of the underlying pathophysiology, the natural history, and the impact on patient's performances. Even though further studies aimed at validating non-pharmacological treatments for spasticity should be fostered, there is growing evidence supporting the usefulness of non-pharmacologic approaches in significantly helping conventional treatments (physiotherapy and drugs) to reduce spasticity and improving patient's quality of life. Hence, non-pharmacological treatments should be considered as a crucial part of an effective management of spasticity.

1. Introduction

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes, which results from an abnormal intra-spinal processing of primary afferent inputs. Such motor disorder follows a central nervous system (CNS) damage that dissociates the motor and sensory components of the diastaltic arch, thus inducing a segmental hyper-excitability [1].

Spasticity can be associated with a variety of symptoms and signs belonging to upper motor neuron syndrome, including clonus, dystonia (muscle constriction in the absence of any voluntary movement), extensor or flexor spasms, spastic co-contraction (contraction of both the agonist and antagonist muscles resulting from an abnormal pattern of commands in the descending supra-spinal pathway), abnormal reflex responses (exaggerated deep tendon reflexes and associated reaction), loss of dexterity, muscle fatigue, weakness, stiffness, fibrosis, and atrophy [2–6].

Many CNS diseases, including stroke, multiple sclerosis (MS), cerebral palsy (CP), and spinal cord injury (SCI), can provoke spasticity. Three main lesion sites have been suggested to induce spasticity: the brainstem, the cerebral cortex (in primary, secondary and supplementary motor areas) and the spinal cord (pyramidal tract) [7]. Of note, spasticity in MS is believed to be due to either axonal degeneration or demyelination within specific descending tracts, or both, thus leading to an inhibitory/excitatory imbalance at spinal network level [8].

Initially, CNS damage determines a local anarchic neuronal reorganization and, as a consequence, a dysfunctional and maladaptive connectivity among several brain structures, including supplementary motor, cingulate motor, premotor, posterior and inferior parietal areas, and cerebellum [9]. These pathologic rearrangements contribute to subcortical hyper-excitability, leading to an increased muscle activity and exaggerated spinal reflex responses to peripheral stimulation [7]. Such hyperactivity may depend on: i) disinhibition of the normal reflex activity (deep ten-

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http://dx.doi.org/10.1016/j.jocn.2017.02.044
0967-5868/

don reflexes and flexor withdrawal reflexes); ii) release of primitive reflexes (e.g., Babinski sign); iii) hyper-active tonic stretch reflex; and iv) muscle fiber metabolic modifications concerning fiber group I (low-oxidative) and II (fast-twitch) [1,10]. In addition, the damage of large networks contributing to cortico-spinal output produces a decreased firing rate at lower motorneurons, and therefore a loss of strength [11]. Consequently, limb immobilization and disuse lead to muscle atrophy, which includes a decline of normal weight-bearing, sarcomeres, skeletal muscle mass, and a reduction in bone mineralization with an accumulation of connective tissue and fat [12,13]. These phenomena further exacerbate the disability and side-effects induced by spasticity.

Moreover, spasticity produces an internal rotation and adduction of shoulder coupled with flexion at the elbow, wrist and fingers, and an adduction and extension of the knee, with equinovarus foot [15,16]. This may also affect the truncal musculature, resulting in poor postural control [16]. Such pathologic postures depend on the imbalance of forces between the agonist and antagonist muscles, affecting the static joint position and dynamic limb movements [16,17].

Even though spasticity has not exclusively negative aspects for the patient, since a paretic limb may allow the patient to continue walking, standing, and transferring, there is a great variety of dramatic short- and long-term negative consequences on daily life activities. In fact, spasticity can *per se* cause a severe disability, owing to: (i) several impairments with body structures or physiological function, such as restricted joint range of movement, loss of dexterity, abnormal limb postures and pain; (ii) activity limitations in limb use, which can interfere with mobility, transfers, and independence with activities of daily; (iii) difficulty with provision of care to an affected limb by the person with MS or their caregivers, such as maintaining palmar hygiene or applying a splint or orthotic; and (iv) restrictions in 'participation' limiting societal roles relating family, work and life situations. Altogether, such issues are very limiting concerning daily life activities and the quality of life (QOL). Therefore, spasticity needs to be carefully assessed and requires an accurate long-term management. A successful treatment of spasticity depends on the clear comprehension of the underlying pathophysiology, the natural history, and the impact on patient's performances.

1.1. When to treat spasticity

Some predictive factors for spasticity development need to be carefully recognized to initiate as soon as possible an adequate treatment. These factors include: (i) a high degree of paresis at stroke onset; (ii) limb hypoesthesia; (iii) more severe paresis at 16 weeks compared to the first week; and (iv) a Modified Ashworth Scale (MAS) of $\geq$2 in at least one joint within 6 weeks after stroke [18,19]. In addition, it has been previously proposed that before treatment is initiated, the following should be considered [13,14]: Does the patient need treatment? What are the aims of treatment? Do the patient and caregivers have the time required for treatment? Will treatment disrupt the life of the patient and caregivers? A striking preliminary consideration consists in the indications and expectations for treatment, as a reduction of leg muscle tone may worsen mobility if tone compensates for leg weakness, allowing the patient to stand. Indeed, careful assessment of the role spasticity plays in substituting for strength (specifically, to facilitate with transfers) is important to avoid decreasing, rather than increasing, function. Manual dexterity and strength also do not improve by reducing muscle tone, which means that treatment of spasticity may not lead to an improvement in function. Hence, the ability of muscles to function after spasticity reduction may vary. Treating spasticity does not always facilitate the acquisition of previously undeveloped skills. As a consequence, clearly identifying the goals of the patient and caregiver is vital. A key factor of spasticity management is the achievement of an individualized, patient-centerd goals, which are set collaboratively with patients, their caregivers, and the rehabilitation team in a functional context [20] and which are a reliable index of a successful outcome, demonstrated in one or more domains of clinical scales [21]. Such goals are derived and prioritized through a multidisciplinary process, where goals are specific, measurable, achievable, realistic and timely [22], and they may be focused on reducing symptoms or impairments, as well as improving the activity level (active and passive function) and the participation and QOL. Patient participation is required to achieve the goals with improvement in the patient's personal potential as a result. To achieve such goals, the following issues should be taken into account: (i) *nursing care*, including preventing or treating contractures and decubitus, body positioning, bladder catheterization, orthotics fitting, facilitating caregiver work, pain management, sleep quality; (ii) *movement improvement*, including unmasking of voluntary movements, accelerating the "spontaneous" recovery process, modifying the "immature" motor pattern, using new recovery techniques to promote guided neuroplasticity, and new functional pattern in moving and walking; (iii) *daily life activities optimization*, including transfers, getting around, putting on clothes, personal hygiene, driving, and so on; (iv) *QOL improvement*, with regard to independent living; and (v) *social and professional reintegration*. In addition, the elimination or avoidance of triggers that can provoke or enhance spasticity (e.g., urogenital infections, constipation, pain) and prevention of complications (including contractures and pressure sores) may also be important [23–25]. Another striking question when treating spastic muscles concerns the impact of their antagonistic muscle groups. While often weak, these muscle groups themselves may be spastic. Treatment of the agonist muscle without treatment of the antagonist muscle may create an additional problem instead of a solution.

In summary, a proper and clear comprehension of the spasticity underlying pathophysiology, its natural history, and the impact of spasticity on patient's performances are of outmost importance to select the most adequate therapeutic option to patient's conditions and goals.

1.2. How to treat spasticity

To treat spasticity, we have currently available a wide repertoire of intervention that can be divided in the following categories: (i) preventative measures; (ii) therapeutic interventions (physical therapy, occupational therapy, hippotherapy, hydrotherapy) and physical modalities (including vibration and electrical currents); (iii) Positioning/orthotics (including taping, dynamic and static splints, wheelchairs, and standers); (iv) oral medications (such as baclofen and dantrolene); (v) injectable neurolytic medications (Botulinum toxins and phenol); and (vi) surgical intervention. For simplicity, we can summarize such approaches into pharmacological and non-pharmacological (Table 1). The former includes oral and injective drugs, while the latter comprehends physical, instrumental, and surgical approaches.

Generally speaking, these categories can be implemented in a neurorehabilitation program [20] by using: (i) uni-disciplinary therapy, e.g. physiotherapy (PhT) or occupational therapy only; (ii) individual pharmacological and non-pharmacological treatment modalities or physical interventions that may form a component of a rehabilitation program; and (iii) multidisciplinary rehabilitation programs involving the provision of a coordinated program by a specialized team of health professionals, delivered by two or more disciplines medical, nursing, physiotherapy, occupational therapy, orthotists, and others.

Table 1
Summarizes the main pharmacologic and non-pharmacologic therapeutic options for spasticity management.

Pharmacologic		Non-pharmacologic	
Non- injectable	Injectable	Instrumental	Non-instrumental
Baclofen	BoNT	Thermotherapy	Surgery
Tizanidine	ITB	Cryotherapy	Neurosurgery
Dantrolene	Neurolysis	Neurorobotic	Orthopedic
Diazepam		ESWT	PT
Gabapentin		NMES	OT
Nabiximols		TENS	
		UsT	
		NINM	
		rTMS	
		tDCS	
		MV	
		WBV	
		FMV	

Legend: BoNT Botulinum neurotoxin; ESWT Extracorporeal Shock Waves Therapy; FES Functional Electric Stimulation; FMV Focal Muscle Vibration; ITB Intrathecal Baclofen; NINM Non-Invasive Neuromodulation; OT occupational therapy; PT physiotherapy; rTMS repetitive Transcranial Magnetic Stimulation; tDCS transcranial Direct Current Stimulation; TENS Transcutaneous Electric Nerve Stimulation; UsT ultrasound therapy; WBV Whole Body Vibration.

PhT and occupational therapy must be always present in a rehabilitative program for both focal and generalized spasticity, and usually include stretching, neurodevelopmental treatment, static positioning, acupuncture, casting, strengthening exercises, Bobath technique, orthotics-splints, and garments [26–34].

Pharmacological treatments may include oral antispastic medications, which must be tailored according to the lesion area and the intended effects. Some treatments aim at directly reducing muscle tone (Dantrolene), whereas others (Baclofen, Tizanidine, Benzodiazepines, Gabapentin, and nabiximols) act on CNS. However, only motor hyperactivity can benefit from drug treatment. Dantrolene acts by binding the ryanodine receptor and affects calcium release, specifically in skeletal muscle, thus inhibiting excitation/contraction coupling and reducing spasticity [35]. Baclofen is a γ-aminobutyric acid (GABA) agonist that binds at the $GABA_B$-receptors of the spinal cord [36]. Tizanidine, an adrenoceptor agonist, increases the pre-synaptic inhibition of motor neurons [37]. Various benzodiazepines, including diazepam and clonazepam, increase the affinity of GABA for the $GABA_A$-receptor complex, leading to an increase in pre-synaptic inhibition and, therefore, a reduction in the excitability of the spinal reflex pathway [38]. Gabapentin is an anti-convulsing structurally similar to GABA, which seems to increase brain levels of GABA [39]. Recently, nabiximols has been employed as an adjunctive treatment for spasticity in MS patients who do not respond satisfactorily to other antispastic drugs [40,41].

There are two main advanced drug treatments. BoNT should be used in key muscles to modify synergic movements and reduce segmental spasticity, beside PhT [42–50]. The Botulinum toxin A (BoNT) is the pharmacological treatment of choice for the management of focal spasticity not responding to non-pharmacological therapy [51]. When BoNT is insufficient to control spasticity and does not contribute to augment QOL and patient's independency, it could be useful to add other therapeutic options, including a large repertoire of non-pharmacological approaches that are well suited to focal and, to some extent, generalized spasticity management.

The intrathecal baclofen (ITB) is a long-term treatment that is delivered by continuous or flexible intra-spinal administration through an implanted pump and reduces spasticity especially in the case of SCI and MS. The usually recommended first test dose is 50 μg in adults, with a maximum dose of 150 μg that should be reached after three days. ITB use should be restricted to people with severe disabling spasticity [52–55].

Neurosurgery and orthopedic surgery (including lengthening operation, tenotomy, neurectomies, transfer of tendons, anterior and posterior rhizotomy, peripheral neurotomy, percutaneous radiofrequency rhizotomy, spinal cord and deep cerebellar stimulation of the superior cerebellar peduncle, and functional neurosurgery) represent secondary therapeutic choices, or sometimes have specific primary indications [56–59]. Spasticity in CP constitutes a different challenge, since it may change as the child grows and develops. Thus, surgery may be postponed to allow a more normal bone and muscle growth. Nonetheless, even though each surgical approach has certain advantages regarding strength and weaknesses, none of these interventions is able to eliminate spasticity [56–59].

All the antispastic drugs have invariably limited effectiveness and are associated with various systemic side effects, such as drowsiness, cognitive impairment and muscle weakness [60–66]. Moreover, each non-pharmacological interventional treatment has not a definitely superior role as compared to the other approaches; instead, the combined multidisciplinary approach gives the best chances of ameliorating spasticity and, eventually, patient's QOL [67–71]. Neurolysis with neurotoxins, chemodenervation, or local anesthetic (i.e., injections of phenol, alcohol, or lidocaine) and BoNT-B are less used.

Beyond the aforementioned cornerstones of spasticity treatments, the present narrative review will summarize the main non-pharmacological intervention approaches in neurorehabilitation setting aimed at reducing spasticity (including Transcutaneous Electric Nerve Stimulation-TENS-, Functional Electric Stimulation -FES-, thermotherapy, cryotherapy, Extracorporeal Shock Waves Therapy -ESWT-, Whole Body Vibration -WBV-, Focal Muscle Vibration -FMV-, repetitive Transcranial Magnetic Stimulation -rTMS-, transcranial Direct Current Stimulation -tDCS-, ultrasound therapy -UsT-, and continuous passive motion through robotic devices) and discuss whether these approaches may represent a potential tool to reduce spasticity by themselves alone or in association with more conventional approaches.

2. Methods for literature search

We reviewed literature on the main non-pharmacological intervention approaches in neurorehabilitation setting aimed at reducing spasticity. A PubMed search of the following terms in different combination with "spasticity": "neuromodulation", "non-pharmachologic intervention", and "combined rehabilitative interventions". The search was limited to human studies and publications written in English, with no restrictions on publication date. The results were further limited to studies focusing on stroke, MS, SCI, and CP. Work screening was accomplished by an initial abstract review and then a full-text assessment of the publications of interest. The reference lists from the publications of interest were examined for other studies that were not identified through the PubMed searches.

3. Non-invasive neuromodulation: an overview

Non-invasive Neuromodulation (NINM) consists in the perturbation of neuronal activities by shaping their synaptic plasticity properties through the application of electromagnetic stimuli, weak currents, or neurochemical agents [72]. Electric currents in case of NINM can be delivered by either electric stimulators, using constant or alternating currents (for tDCS), or magnetic stimulators (for TMS). The induced currents may affect the synaptic and non-synaptic plasticity (i.e., the ability of synapses to strengthen or

weaken over time in response to increases or decreases in their activity) by modifying the polarity of neuronal membrane and inducing long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity, or spike-time dependent plasticity phenomena. Such processes depend on several mechanisms, including axonal or depolarizing blockade, stochastic normalization or reduction of neural firing, and modulation of neural network oscillations [73,74].

TMS is a NINM technique that allows exploring various neural processes and treating a variety of neuropsychiatric illnesses. It is based on the Faraday's principle of electromagnetic induction of an electric field in a discrete brain region [75–77]. Single-pulse stimulation techniques can measure cortical inhibition, facilitation, reactivity, and cortical plasticity, providing valuable insights into the cortical physiology. The repetitive or patterned application of magnetic stimuli (e.g. rTMS) induces changes in cortical excitability at the site of stimulation, and trans-synaptically at distant sites, and this is currently being used to investigate several neurophysiologic processes and treat some neurologic and psychiatric disorders such as stroke, depression, and schizophrenia [76,77]. Specifically, rTMS induces lasting inhibitory or facilitatory aftereffects on corticospinal motor output, probably thanks to LTD- and LTP-like mechanisms, beyond the shifting in network excitability, activation of feedback loops, and activity-dependent metaplasticity phenomena [78–81]. The latter are key elements for the successful use of combined therapeutic approaches including NINM and other techniques (e.g., Neurorobotic, PhT, and FMV). In this case, previous synaptic activities influence the level of reactivity to subsequent stimuli. In particular, a preceding post-synaptic high firing would elevate the threshold for LTP induction and would lower the threshold for LTD. On the other hand, a low post-synaptic firing would promote the opposite [78–81]. Therefore, a priming (i.e. a synaptic strength modifying intervention) may change various synaptic properties so to alter the effects of a subsequent plasticity-inducing event (conditioning). Priming and conditioning can take the form of behavioral, environmental, pharmacological, or electrophysiological input [78–81]. Notably, both the TMS and rTMS are safe and well tolerated, except for a potential risk of seizures when employing high-frequency stimulation [82].

tDCS is a NINM technique consisting in the application of low amplitude direct electrical current (1–2 mA) through pad electrodes placed on the scalp. The term direct means that the electrical flow travels from one electrode (anode, positive electrode) to the other (cathode, negative electrode). tDCS can induce prolonged increase or decrease in cortical excitability of the underlying brain area (according to the orientation of dendrites and axons in the electrical field), which outlasts the period of stimulation [83–85]. Notably, tDCS modulates the spontaneous neuronal firing rates and synaptic and non-synaptic plasticity, thus resulting in changes in resting polarization of neurons, but this does not trigger an action potential, due to the low current density delivered [86].

Thanks to their neuroplasticity properties and their effects on neuronal excitability at both short- and long-lasting intervals, rTMS and tDCS can modulate neural circuitry at both brain and spinal level, thus reshaping local and distant excitability with a tangible effect on focal and limb spasticity. rTMS has been satisfactorily applied in MS, stroke, SCI, and CP induced spasticity, whereas tDCS has been mainly employed in post-stroke spasticity, whereas generalized spasticity has been less investigated [87–89].

3.1. rTMS in the rehabilitative setting

High-frequency rTMS (5 Hz, 10 sessions for two weeks, 900 pulses per session in 15 min, 1 Hz-controlled) [90] and intermittent theta-burts (iTBS) protocols (10 sessions for 2 weeks, ten bursts of 600 pulses, placebo-controlled) [87], applied to the primary motor area in relapsing-remitting MS patients, have shown an improvement in lower limb spasticity lasting from a week up to a month, as measured by MAS score (reduction), H-reflex amplitude (i.e., reduction of spasticity-related spinal hyper-excitability), and MEP amplitude (increase) [87,88,90,91], even when combined with PhT [92]. 1 Hz rTMS had opposite effects [90]. Based on these two works, magnetic stimulation, either rTMS or iTBS, on the affected brain area might have a lasting therapeutic effect in MS spasticity.

In patients with incomplete SCI, high-frequency rTMS induced a significant reduction in the spasticity in the lower extremities [93,94]. In particular, 20 Hz-rTMS on the vertex for 5 days led only to a MAS reduction up to one week, but neither an amelioration in SCI-related spasticity evaluation tool (SCI-SET) nor changes in neurophysiological examinations, including H reflexes or MEP amplitude, were evidenced [93,94]. Therefore, one may argue that high-frequency rTMS could improve spasticity and motor function in SCI, although there are some contradicting reports [95].

Valle et al. [96] evaluated the effects of 5 Hz-rTMS for 5 days on upper limb spasticity in patients with CP. 5 Hz-rtMS failed in improving spasticity clinically measured but led to a partial improvement in range of movement. Of note, the authors tested also the 1 Hz-TMS, which was totally ineffective. Such findings were confirmed by a recent clinical trial, demonstrating that only the association between high-frequency-rTMS and PhT reduced significantly the spasticity in upper and lower limbs as compared to PhT or rTMS [97].

The effect of rTMS have been largely studied in patients with post-stroke severe spasticity in the subacute or chronic phase (from few months to 20 years) [98–104]. Generally speaking, rTMS can be used to target: (i) both the hemispheres; (ii) the healthy hemisphere when a twitch is visible in the affected limb by stimulating each hemisphere or when it could induce movement in the paretic arm; and (iii) the affected hemisphere when there is a residual twitch. Two main approaches have been used: (i) a low-frequency rTMS over the unaffected hemisphere [99–108]; and (ii) a 10 Hz-rTMS over the affected hemisphere [104]. Low frequency rTMS over both hemispheres yielded a spasticity reduction in upper limb for more than 1 month in chronic stroke patients, whereas movement improvement was only achieved by suppressing the healthy hemisphere [99].

Similar results were obtained by other studies in chronic stroke phase [103], dealing with NINM coupled with occupational therapy [100,105–107], and with occupational therapy during 100 mg/day levodopa administration [106]. Instead, Etoh et al. [108] failed to show change in spasticity, measured with MAS, in chronic patients. A paired approach between 1 Hz (50-s periods over the unaffected hemisphere) and 10 Hz-rTMS (5-s periods over affected hemisphere) induced significant improvement in spasticity, as measured by MAS. Noteworthy, a study testing high frequency rTMS on the unaffected hemisphere delivered by alone, found instead a spasticity increase. Last, 1 Hz-rTMS (for at least 5 days) in chronic stroke has been confirmed as effective in reducing spasticity in upper limb up to one week when applied by alone or in parallel to PhT [109–111].

3.2. tDCS in the rehabilitative setting

There are no convincing evidences about the effect of tDCS on spasticity in MS [112] and CP [113] (where only short-lasting improvement has been reported). On the other hand, tDCS application in SCI patients focused on pain reduction. In analogy with the role of rTMS frequency in orienting TMS aftereffects, the polarity of tDCS [113–115] may influence the effects on spasticity when triggering either the affected or unaffected hemisphere. tDCS has been

applied only in chronic post-stroke patients. Cathodal tDCS, which yields inhibitory effects, induced a spasticity improvement in post-stroke paretic proximal upper limb when applied over unaffected motor cortex, also with conventional physical therapy [116]. The combined approach (anodal tDCS over affected hemisphere and cathodal tDCS over the unaffected one for five days, 20 min/day), applied by alone [114] or combined with robotic therapy [115] in upper limb chronic stroke, raised a more significant improvement in spasticity (by MAS) for the left than the right upper limb. Nonetheless, such studies did not offer convincing evidence that tDCS can improve spasticity in people with stroke [116,117].

3.3. New NINM targets

New recent NINM approaches targeted spinal roots, nerves, and muscles [118]. Spinal tDCS have been successfully used in reducing spasticity in ankle plantar flexor muscles in SCI [119]. Further, given that homosynaptic depression is characteristically decreased in spastic patients, spinal tDCS might be a promising tool to improve spasticity [120]. The magnetic stimulation of peripheral nerve induces a strong recruitment of neural networks involved in motor control by mainly activating the proprioceptive afferents in CP [121]. Concerning SCI, the unilateral paravertebral repetitive magnetic stimulation may reduce the spastic tone increase of the lower limb [122]. However, more studies are needed to clarify the usefulness of such approaches in treating spasticity.

3.4. Summary

NINM seems to be a promising intervention to reduce spasticity in patients with MS, stroke, CP and SCI. Concerning stroke, we may conclude that low-frequency rTMS over unaffected hemispheres could be effective in the reduction of spasticity when applied both in parallel to conventional therapies (increasing conventional therapy outcome) and by alone (leading to a significant MAS reduction). Nonetheless, rTMS effects are sensible to the triggered hemisphere and the underlying pathophysiology of lesion, and as both a unique intervention and in combination with medical or physical therapy, which augment the effects of NINM. In addition, because of seizure potential risk with high-frequency rTMS [82], the "inhibitory" low-frequency rTMS is generally preferred. As compared to rTMS, there are currently less evidences supporting the role of tDCS in treating post-stroke spasticity. Although rTMS on spasticity in stroke patients seems effective, a few studies employed sham-rTMS as control group [103,108]. Therefore, further studies may be needed to confirm rTMS efficacy in stroke patients. Similarly, the role of rTMS and tDCS in MS, CP, and SCI spasticity should be better defined.

4. Other approaches

4.1. TENS

TENS is a form of electrical stimulation (usually delivered as asymmetrical biphasic modified square wave pulses) that is used at high frequencies for pain relief [123]. TENS machine is wired to two electrodes that can be placed on the target skin area, thus creating a circuit of electrical impulses traveling along the nervous fibers [124,125]. Nonetheless, TENS is also administered at very low frequencies (sensory level TENS, 2–10 Hz) to specifically target sensory nerve fibers, avoiding muscle contraction. In this way, sensory stimulation would induce the release of β-endorphins that in turn decrease motorneuron excitability and gate incoming inputs [126,127], thus reducing segmental hyper-excitability. In addition, backwards inputs from spinal cord to sensory areas may reshape cortical synaptic plasticity, influencing the descending projections onto spinal cord and further modulating segmental hyperexcitability [126,127]. The optimal stimulation parameters must be set according to the comfort and the results obtained by the patient, thus regulating current intensity (up to 80 mA), pulse frequency (up to 150 Hz) and duration (up to 250 ms), stimulation type (burst −2/3 burst/s- or modulation), number of channels to be employed (usually two), frequency and length of application (one/twice per day, up to 4 consecutive weeks). Indeed, recent case-control studies employing TENS for spasticity management (as compared to placebo, another TENS protocol, or another intervention) showed that TENS is a useful adjunctive intervention for spasticity management (as measured by MAS) as well as for functional improvement (e.g., gait) [124]. Specifically, using PhT combined with TENS has been shown to reduce spasticity and increase walking ability in chronic stroke and SCI [124,125,127–130]. Instead, there are no significant evidences for TENS benefit in MS patients [126], albeit two studies on high-frequency TENS reported a satisfactory improvement of fatigue, spasticity, bladder control, and overall QOL [131–134].

4.2. NEMS

Neuromuscular Electrical Stimulation (NMES) delivers small electrical impulses directly to the nerves of the affected muscles, and forces functional movements when provided at high frequencies (20–50 Hz) (that produce muscle tetany and contraction) [135]. NMES is called Functional Electrical Stimulation (FES) when paired to a motor task, so that FES can be used to generate muscle contraction in otherwise paralyzed limbs to produce functional movement, such as grasping, walking, bladder voiding, standing.

The anti-spastic effects of NMES, when it leads to muscle contraction (i.e. when employing rectangular waves or Faradic stimulation), may depend on the facilitation of Renshaw cell recurrent inhibition, antagonist reciprocal inhibition, cutaneous sensory habituation, modification of visco-elastic muscle properties, modulation of muscle spindles activity, and augmentation of Ib-fiber activation [136–142]. In particular, the intent of applying NMES to antagonist muscles is to strengthen reciprocal inhibition through the spinal reflex loop [142–146]. Thus, NMES may facilitate neurorehabilitation inhibitory techniques and promote neuroplasticity during long-term applications [142–146]. Indeed, plastic effects within some spinal cord pathways may be a possible mechanism associated with the NMES-induced spasticity improvement [146]. As limitation factor, NMES can induce muscle fatigue [147–149], since it: (i) can alter the normal motor unit recruitment order; (ii) can produce sudden, uncoordinated, inefficient movement patterns rather than the smooth gradation of force; (iii) can difficultly activate deeper parts of a muscle; and (iv) could not have long-term effectiveness following discontinuation. In addition, the use of cyclic-FES may enable persons to actively perform task-oriented movements, dependently of patient cooperation [150–156].

Both FES and NMES have showed the capacity for clinically reducing spasticity in different neurologic conditions, including stroke, CP, and incomplete SCI [157–164], when applied on the motor point in twice a day 30-min sessions, five days per week for at least four weeks, in parallel to conventional physiotherapy, lower extremity cycling protocols or Neurorobotic [153,156,163,164]. Notably, it has been demonstrated that NMES can induce a significant MAS decrease while directly stimulating agonist muscles. However, a dramatic decrease in agonist muscle tone can be obtained by stimulating the antagonist muscles [157–164].

Recently, a variant of NEMS, called balanced-charge kHz frequency alternating current, has been shown to rapidly and reversi-

bly block nerve conduction, thus being of potential usefulness in reducing segmental spasticity [165].

4.3. Whole body vibration

WBV consists in the repetitive perturbation of the whole body through vibrating plates on which the patient stands. It is possible to manipulate frequency (i.e., the number of complete cycles per second), amplitude (the amount of displacement measured in mm), and direction (vertical displacement or a side-to-side alternating vertical sinusoidal vibration) of the vibration. In particular, the vertical vibration creates a uniform amplitude throughout the vibration plate, whereas the sinusoidal vibration increases the amplitude going from the pivoting fulcrum at the center of the vibration plate [166]. Nonetheless, the exact action of this therapy is yet poorly understood [166]. It has been proposed that muscle spindles and alpha motor neurons could be stimulated by the vibrations, which initiates a muscle contraction, also leading to local, short-term metabolic effects [167–170]. WBV has been demonstrated to be effective in ameliorating force, fatigue, spasms, pain, activities of daily life, social functioning, stiffness, gait, body movement, and emotional health, but without significant effects on spasticity [171,172] owing to different neurologic conditions, including stroke, MS, and CP [173,174]. Nevertheless, WBV combined with other approach could decrease spasticity, with beneficial effects on walking speed and motor development in spastic diplegia due to CP and SCI [172–184].

4.4. Focal vibration

FV has been successfully employed in managing focal spasticity and has stronger but non-diffused anti-spastic effects as compared to WBV [185–191]. FV is delivered through mechanical device and consists in the administration of low-amplitude/high-frequency vibratory stimuli to specific muscle or tendon targets [192,193]. FV on a tendon or muscle preferentially perturbs primary (Ia) spindle afferents and Golgi tendon organs [193–198], resulting in inhibition of the monosynaptic reflex (due to presynaptic inhibition increase, and modifications within reciprocal and recurrent inhibition), and, consequently, reducing the spasticity entity [199–201], as measured by clinical (MAS) and electrophysiological markers (H-reflex). Further, the positive results offered by FMV on spasticity may also depend on the induction of strong plasticity changes at sensory-motor cortex level [196–198]. In fact, the aforementioned inputs reach both the primary somatosensory (SI) and primary motor cortex (M1). To this end, it has been argued that Ia-inputs could alter the excitability of the cortico-spinal pathway by modulating intra-cortical inhibitory and facilitatory phenomena within M1 [197,198]. The specific pattern of direct connections linking SI and M1 may provide the anatomical substrate for the effects of MV in the reorganization of these areas [194–198].

Several studies have been performed to investigate the antispastic effect of focal muscle vibration in patients with stroke [185,187,202–208]. In addition, it has also been reported that vibratory stimulation of the hemiplegic lower limb increased gait speed in stroke patients [206]. Although all clinical studies reported favorable results of vibration therapy on spasticity or motor function, the stimulation parameters varied, ranging from 50 to 120 Hz in frequency and 0.01–1 mm in amplitude. Therefore, effective parameters of vibration need to be established to develop a novel therapeutic approach for use in clinical practice [207]. On the other hand, different electrophysiological effects of FV were verified during muscle belly or tendon vibration: it has been reported that muscle FV may be more effective than tendon FV for reducing spinal hyper-excitability. Interestingly, FMV has been shown to be further efficacious in increasing force, ameliorating multi-joint control, and reducing pathological synergies, spasticity, and spastic co-contraction in diverse neurologic conditions when paired with different other treatments, including constraint-induced movement therapy, FES, and intensive robot-assisted repetitive movements [209–214]. This increased efficacy may depend on greater plasticity effects ascribable to a sort of associative plasticity between motor practice and the continuous proprioceptive inputs offered by MV, as compared to motor practice or FV alone [193].

In individuals with SCI, weekly FV resulted in a short-term spasticity reduction and a H-reflex inhibition lasting for a maximum of 24^{hh}, whereas WBV resulted in a decrease in spasticity lasting for 6–8 days after the last vibration session. Although WBV and FV might decrease spasticity for a short period, no evidence-based recommendation can be drawn from the literature to guide rehabilitation medicine clinicians to manage spasticity with vibration application [186].

Concerning CP, MV was applied for 3 consecutive days, 30 min/-day, with fixed frequency (100 Hz) and low amplitude (<0.5 mm peak-to-peak), on lower limbs. A significant MAS reduction was observed up to 12 weeks after the end of the treatment. MV may thus be a noninvasive and cost-effective setting of treatment for spasticity due to CP [215,216].

4.5. Extracorporeal shock-wave therapy

Shock waves are defined as a sequence of single sonic pulses characterized by high peak pressure (100 MPa), fast pressure rise (<10 μs) and short duration (10 μs) [217–219]. The mechanisms through which ESWT could induces changes within tissue remain uncertain, but ESWT may entrain a cascade of interactions between physical shock wave energy and biologic responses, including the expression of angiogenesis-related growth factors such as endothelial nitric oxide synthase, vessel endothelial growth factor, and proliferating cell nuclear antigen and neovascularization [220–223]. It has been suggested that the fibrosis and the rheological components of the hypertonic muscles may be the target of ESWT [224–228]. In addition, ESWT may induce enzymatic nitroxide synthesis that would be involved in neurotransmission and synaptic plasticity [226–228].

Beyond different applications in many orthopedic diseases (and kidney stones), ESWT has been proposed for the treatment of abnormal muscle tone, since some studies have proved a reduction in MAS, an improvement in motor performance, and an increase in range of movement and the degree of perceived benefit in stroke patients, when applying ESWT in forearm flexor or hand interosseous, and Plantar flexor muscles and in CP when stimulating spastic plantar flexor muscles [217–219,224–227,229–233].

4.6. Ultrasound therapy

UsT has thermal and mechanical effects on the target tissues, resulting in an increased local metabolism, circulation, extensibility of connective tissue, and tissue regeneration [234–236]. UsT does not only induce viscoelastic changes in spastic muscles, but also decreases the sensitivity of the muscle spindle to stretching and α-motorneuron excitability by increasing the tissue temperature [234–236].

Studies performed in post-stroke patients have demonstrated that UsT (fifteen 10-min sessions over a 5-week period; frequency 1 MHz; intensity 1.5 W/cm^2) may significantly reduce spasticity (as measured by MAS) maybe through a significant α-motorneuron excitability decrease [234–238]. On the other hand, a recent paper compared the efficacy of UsT and infrared therapy in the management of spasticity, reporting that neither infrared nor UsT reduced electrophysiological and clinical measures of

spasticity [239]. On the contrary, a comparison among UsT, TENS, and BoNT-A in the treatment of spastic equinus in adults with chronic stroke showed that botulinum toxin type A is more effective than therapeutic ultrasound and TENS [240]. There are no currently available studies concerning the application of UsT in SCI, MS, or CP spasticity.

4.7. Cryotherapy and thermotherapy

The local cooling of spastic muscles could be considered a useful and inexpensive tool that could be combined with active training of the antagonist muscles, and this can also be used to hinder muscle hypertonia and clonus during casting procedures. Indeed, cryotherapy applied for 20 min with cold packs at −12 °C or for more than 20 min by means of cold air temporarily decreases spasticity and clonus, mainly by reducing the sensitivity of low-threshold afferents and muscle spindles to stretching in chronic stroke and SCI [241–244]. In particular, cryotherapy (cooling) was reported to exhibit a transient beneficial effect on elevated muscle tone, while hydrotherapy has been suggested to reduce spasticity and the need for ITB in patients with SCI [245,246]. Last, cold balneotherapy with sulphurous water may be of some help in reducing upper limb spasticity in post-stroke patients [247].

It has been suggested that the thermotherapy anti-spastic effects may depend on the relaxation of muscles and soft tissues and a decrease in γ-afferent fiber activity, which would lead to a decrease of the inputs coming from muscle spindles, with a consequent inhibition of the inputs to α-fibers and a reduction of the response of muscle spindles to stretching [248–251]. Thermotherapy by means of hot water (41 °C) applied for 10 min [253] has been reported to decrease muscle tone, reduce muscle spasms, and increase the pain threshold in patients with muscle hypertonia [248–252].

There are no currently available studies concerning the application of cryotherapy and thermotherapy in post-SCI, MS, or CP spasticity.

5. Neurorobotic

Convincing evidence suggests a substantial improvement in spasticity of the paretic limb after robot-assisted neurorehabilitation, beyond strength, motor ability, movement smoothness, muscle trophism, and osteoporosis amelioration [254–259]. The mechanism through which Neurorobotic may reduce spasticity are still unclear. Continuous motion during intensive, repetitive, and task-oriented exercises may somehow reduce spinal hyperexcitability. In addition, it has been proposed that robotic rehabilitation may induce a spasticity reduction by activating spinal reciprocal inhibition mechanisms in the antagonist muscles [259]. Indeed, the high-intensity treated patients showed a reduction of spasticity measured by MAS than the low-intensity treated patients did, whereas motor functions were not significantly different between the two groups at the follow-up [259].

Robotics has been shown to ameliorate spasticity mainly in stroke and SCI, by themselves alone [255,260–263], in association with BoTN, PhT, antispastic drugs, and NMES [164,264–267], whereas other works reported non-significant effects by alone or in association with BoNT in stroke and MS [264,268–273] or supported robotic as a useful add-om treatment [257], even in the acute phase [274]. In addition, as previously acknowledged, robotic neurorehabilitation can be potentiated by the concomitant or coupled use of NINM [275–279] and FMV [280–282] so to further improve motor performance, QOL, cognitive function and spasticity, as compared to separately-applied methods. Such increased efficacy may depend on a greater plasticity effect ascribable to a sort of associative plasticity between motor practice during robotic neurorehabilitation and the concomitant or primer plastic contribution offered by NINM and FMV [283–284].

6. Discussion

Our review suggests the overall effectiveness of non-pharmacologic instrumental interventions in a multidisciplinary setting (i.e., including PhT and occupational therapy, which should be always included in Neurorehabilitative programs) in different neurological conditions, including MS and stroke [62,63,285]. Although different in nature, all abovementioned non-pharmacologic intervention approaches may achieve spasticity reduction through changes in the viscoelastic properties of the connective tissue, altering the neural patterns of spasticity or spasms, and maintaining levels of function for the individual [60,63].

Nonetheless, there is no sufficient evidence so far to state that a specific approach is more effective than other in minimizing spasticity. Indeed, protocol choice should be case-by-case guided, depending on spasticity etiology, patient's age, spasticity severity, and the common goals of (i) relieving the signs and symptoms of spasticity, (ii) reducing the pain and frequency of muscle contractions; (iii) improving gait, hygiene, activities of daily living, and ease of care; (iv) reducing caregiver challenges such as dressing, feeding, transport, and bathing; (v) improving voluntary motor functions involving objects such as reaching for, grasping, moving, and releasing; and (vi) enabling more normal muscle growth in pediatrics. Functional outcomes, however, remain to be better characterized and predictors of response need to be identified to guide clinical decision making.

Specifically, our data show that non-pharmacological instrumental intervention may be of some help in managing mild to moderate focal spasticity in different neurologic conditions. Different interventions, including Neurorobotic, rTMS, and electric currents may reduce spasticity by alone (although robotic devices need further research to show their suitability for spasticity management, with particular regard to severe spasticity), but their effects increase when paired to other approaches, with particular regard to PhT. To this end, the use of FES/NMES combined with different PhT strategies has shown to result in some spasticity improvements in hemiplegic patients. NINM seems particularly promising. In fact, low-frequency rTMS on the healthy hemisphere could decrease spasticity depending on a reshape on interhemispheric inhibition from the healthy to affected hemisphere and of the abnormal maladaptive plasticity within the affected hemisphere, and on the underlying neurological pathology, as a unique intervention or combination with medical and/or physical therapy. Nonetheless, sham-rTMS as control group has not been employed, except few studies. Therefore, further studies may be needed to confirm its efficacy in stroke patients. Studies in CP, SCI, and MS are still unfortunately limited, but NINM seems to be a promising intervention to reduce spasticity. Instead, tDCS has shown too variable effects depending on the severity of spasticity and/or underlying neurological disorder. Thus, the clinical applicability of tDCS needs to be confirmed in well-designed trials with bigger sample size and longer-term follow-up.

In case of severe focal spasticity or when conventional and instrumental non-pharmacological approaches give insufficient results, it would be necessary to use injective pharmacological treatments as a primer, and then continue conventional and instrumental non-pharmacological approaches. Last, generalized spasticity nearly always need pharmacological treatments as a primer. Therefore, pharmacological and non-pharmacological interventions would work together to manage generalized spasticity and

refractory spastic areas, or to potentiate drug effect. In the most severe, refractory, and selected cases there could be a place for surgical intervention [63].

Future research should be fostered to deeper analyze the impact of non-pharmacological interventions on spasticity and the correlated functional outcomes, since the current studies on these treatments are non-homogeneous in methodology, population, intervention, and outcomes [286–288]. We argue that the main character in the research field should the assessment of brain plasticity, which has a well-known key role in function restore and adaptation, as well as in spasticity [289], in order to adapt treatment resources to meet the needs of each patient and to optimize the recovery process.

Conflicts of interest

The authors report no conflicts of interest.

References

[1] Trompetto C, Marinelli L, Mori L, et al. Pathophysiology of spasticity: implications for neurorehabilitation. Biomed Res Int 2014;2014:354906.
[2] Mullick AA, Musampa NK, Feldman AG, et al. Stretch reflex spatial threshold measure discriminates between spasticity and rigidity. Clin Neurophysiol 2013;124:740–51.
[3] Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koella WP, editors. Spasticity: disordered control. Chicago: Yearbook Medical; 1980. p. 485–94.
[4] Tardieu G, Tardieu C, Colbeau Justin P, et al. Effects of muscle length on an increased stretch reflex in children with cerebral palsy. J Neurol Neurosurg Psychiatry 1982;258:348–52.
[5] Rymer WZ, Houk JC, Crago PE. Mechanisms of the clasp-knife reflex studied in an animal model. Exp Brain Res 1979;37:93–113.
[6] Kamper DG, Schmit BD, Rymer WZ. Effect of muscle biomechanics on the quantification of spasticity. Ann Biomed Eng 2001;29:1122–34.
[7] Mukherjee A, Chakravarty A. Spasticity mechanisms for the clinician. Front Neurol 2010;1:149.
[8] Kheder A, Nair KP. Spasticity: pathophysiology, evaluation and management. Pract Neurol 2012;12:289–98.
[9] Lim JS, Kang DW. Stroke connectome and its implications for cognitive and behavioral sequela of stroke. J Stroke 2015;17:256–67.
[10] Thibaut A, Chatelle C, Ziegler E, et al. Spasticity after stroke: physiology, assessment and treatment. Brain Inj 2013;27:1093–105.
[11] Reinkensmeyer DJ, Guigon E, Maier MA. A computational model of use-dependent motor recovery following a stroke: Optimizing corticospinal activations via reinforcement learning can explain residual capacity and other strength recovery dynamics. Neural Netw 2012:60–9.
[12] Berg HE, Larsson L, Tesch PA. Lower limb skeletal muscle function after 6 weeks of bed rest. J Appl Physiol 1997;82:182–8.
[13] Ferretti G, Berg HE, Minetti AE, et al. Maximal instantaneous muscular power after prolonged bed rest in humans. J Appl Physiol 2001;90:431–5.
[14] Tizard JP. Cerebral palsies: treatment and prevention. The Croonian lecture 1978. J R Coll Physicians Lond. 1980 Apr. 14(2):72–7,80.
[15] Hefter H, Jost WH, Reissig A, et al. Classification of posture in post-stroke upper limb spasticity: A potential decision tool for botulinum toxin A treatment? Int J Rehabil Res 2012;35:227–33.
[16] Marciniak C. Post-stroke hypertonicity: upper limb assessment and treatment. Top Stroke Rehabil 2011;18:179–94.
[17] Sheean G. Pathophysiology of spasticity. In: Sheean G, editor. Spasticity Rehabilitation. London: Churchill Communications Europe LTD; 1998. p. 17–38.
[18] Urban PP, Wolf T, Uebele M, et al. Occurence and clinical predictors of spasticity after ischemic stroke. Stroke 2010;41:2016–20.
[19] Coupar F, Pollock A, Rowe P, et al. Predictors of upper limb recovery after stroke: a systematic review and metaanalysis. Clin Rehabil 2012;26:291–313.
[20] Steins S, O'Young B, Young M. Person-centred rehabilitation: interdisciplinary intervention to enhance patient enablement. In: O'Young B, Young M, Steins S, editors. Physical Medicine and Rehabilitation Secrets. USA: Hanley & Belfus; 2002. p. 4–9.
[21] Petropoulou KB, Panourias IG, Rapidi CA, et al. The importance of neurorehabilitation to the outcome of neuromodulation in spasticity. Acta Neurochir Suppl 2007;97:243–50.
[22] Wade DT, Bovend'Eerdt TJH. How to set SMART goals. Clin Rehabil 2010;24 (4):382.
[23] Henze T, Rieckmann P, Toyka KV. Symptomatic treatment of multiple sclerosis (Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society). Eur Neurol 2006;56:78–105.
[24] Rekand T. Clinical assessment and management of spasticity: a review. Acta Neurol Scand 2010;190:62–6.
[25] Bagherpour R, Dykstra DD, Barrett AM, et al. A comprehensive neurorehabilitation program should be an integral part of a comprehensive stroke center. Front Neurol 2014;5:57. http://dx.doi.org/10.3389/fneur.2014.00057.
[26] Bovend'Eerdt TJ, Newman M, Barker K, et al. The effects of stretching in spasticity: a systematic review. Arch Phys Med Rehabil 2008;89:1395–406.
[27] Watt J, Sims D, Harckham F, et al. A prospective study of inhibitive casting as an adjunct to physiotherapy for cerebral-palsied children. Dev Med Child Neurol 1986;28:480–8.
[28] Morris SL, Dodd KJ, Morris ME. Outcomes of progressive resistance strength training following stroke: a systematic review. Clin Rehabil 2004;18:27–39.
[29] Sunnerhagen KS, Olver J, Francisco GE. Assessing and treating functional impairment in post-stroke spasticity. Neurology 2013;80:S35–44.
[30] Bobath B. The application of physiological principles to stroke rehabilitation. Practitioner 1979;223:793–4.
[31] Neuhaus BE, Ascher ER, Coullon BA, et al. A survey of rationales for and against hand splinting in hemiplegia. Am J Occup Ther 1981;35:83–90.
[32] Basaran A, Emre U, Karadavut KI, et al. Hand splinting for post-stroke spasticity: a randomized controlled trial. Top Stroke Rehabil 2012;19:329–37.
[33] Watanabe T. The role of therapy in spasticity management. Am J Phys Med Rehabil 2004;83:S45–9.
[34] Gracies JM. Physical modalities other than stretch in spastic hypertonia. Phys Med Rehabil Clin N Am 2001;12:769–92.
[35] Zhao F, Li P, Chen SR, et al. Dantrolene inhibition of ryanodine receptor Ca2+ release channels. Molecular mechanism and isoform selectivity. J Biol Chem 2001;276:13810–6.
[36] Hulme A, MacLennan WJ, Ritchie RT, et al. Baclofen in the elderly stroke patient its side-effects and pharmacokinetics. Eur J Clin Pharmacol 1985;29:467–9.
[37] Wagstaff AJ, Bryson HM, Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs 1997;53:435–52.
[38] Olvey EL, Armstrong EP, Grizzle AJ. Contemporary pharmacologic treatments for spasticity of the upper limb after stroke: a systematic review. Clin Ther 2010;32:2282–303.
[39] Formica A, Verger K, Sol JM, et al. Gabapentin for spasticity: a randomized, double-blind, placebo-controlled trial. Med Clin (Barc) 2005;124:81–5.
[40] Centonze D. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity nervous pathways. Eur Neurol 2014;72:6–8.
[41] Russo M, Calabrò RS, Naro A, et al. Sativex in the management of multiple sclerosis-related spasticity: role of the corticospinal modulation. Neural Plast 2015;2015:656582.
[42] McCrory P, Turner-Stokes L, Baguley IJ, et al. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multicenter randomized placebo-controlled study of the effects on quality of life and other person-centered outcomes. J Rehabil Med 2009;41:536–44.
[43] Simon O, Yelnik AP. Managing spasticity with drugs. Eur J Phys Rehabil Med 2010;46:401–10.
[44] Bakheit AM, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke 2000;31:2402–6.
[45] Simpson DM, Gracies JM, Graham K, et al. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Neurology 2009;73:736–8.
[46] Burbaud P, Wiart L, Dubos JL, et al. A randomized, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. J Neurol Neurosurg Psychiatr 1996;61:265–9.
[47] Simpson DM, Gracies JM, Yablon SA, et al. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatr 2009;80:380–5.
[48] Pedreira G, Cardoso E, Melo A. Botulinum toxin type A for refractory post-stroke shoulder pain. Arq Neuro Psiquiatr 2008;66:213–5.
[49] Sheean G, Lannin NA, Turner-Stokes L, et al. Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: international consensus statement. Eur J Neurol 2010;17:74–93.
[50] De Paiva A, Meuniere FA, Molgo J, et al. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci U S A 1999;16(96):3200–5.
[51] Stevenson VL. Spasticity management. Clin Rehabil 2010;24:293–304.
[52] Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. J Neurosurg 1992;77:236–40.
[53] Van Schaeybroeck P, Nuttin B, Lagae L, et al. Intrathecal baclofen for intractable cerebral spasticity: a prospective placebo-controlled, double-blind study. Neurosurgery 2000;46:603–9.
[54] Stempien L, Tsai T. Intrathecal baclofen pump use for spasticity: a clinical survey. Am J Phys Med Rehabil 2000;79:536–41.
[55] Harned ME, Salles SS, Grider JS. An introduction to trialing intrathecal baclofen in patients with hemiparetic spasticity: a description of 3 cases. Pain Physician 2011;14(5):483–9.
[56] Farmer JP, Sabbagh AJ. Selective dorsal rhizotomies in the treatment of spasticity related to cerebral palsy. Childs Nerv Syst 2007;23:991–1002.
[57] Siegfried J, Lazorthes Y, Broggi G, et al. Functional neurosurgery of cerebral palsy. Neurochirurgie 1985;31:1–118.

[58] Chambers HG. The surgical treatment of spasticity. Muscle Nerve Suppl 1997;6:S121–128.
[59] Maarrawi J, Mertens P, Luaute J, et al. Long-term functional results of selective peripheral neurotomy for the treatment of spastic upper limb: prospective study in 31 patients. J Neurosurg 2006;104:215–25.
[60] Khan F, Gray O. Disability management and rehabilitation for persons with multiple sclerosis. Neural Regener Res 2010;5:301–9.
[61] Turner-Stokes L, Pick A, Nair A, et al. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. Cochrane Database Syst Rev 2015;12. CD004170.
[62] Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet 2011;377:1693–702.
[63] Lockley LJ, Buchanan K. Physical management of spasticity. In: Stevenson VL, Jarrett L, editors. Spasticity Management: a Practical Multidisciplinary Guide. London: Informa Healthcare; 2006. p. 37–58.
[64] Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7:1–111.
[65] Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. Cochrane Database System Rev 2003;4.
[66] Montané E, Vallano A, Laporte JR. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 2004;63(8):1357–63. Review.
[67] Bethoux F. Spasticity management after stroke. Phys Med Rehabil Clin N Am 2015;26(4):625–39.
[68] Amatya B, Khan F, La Mantia L, et al. Non pharmacological interventions for spasticity in multiple sclerosis (Review). Cochrane Database Syst Rev 2013;28 (2). CD009974.
[69] Ganesan V. Outcome and rehabilitation after childhood stroke. Handb Clin Neurol 2013;112:1079–83.
[70] Rekand T, Hagen EM, Grønning M. Tidsskr Nor Laegeforen. B Spasticity following spinal cord injury. 2012;132(8):970–3.
[71] Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal cord injury. World J Orthoped 2015;6(1):24–33.
[72] Katz PS, Calin-Jageman RJ. Neuromodulation. In: Squire LR, editor. Encyclopedia of Neuroscience. London: Elsevier; 2009. p. 497–503.
[73] Mozzachiodi R, Byrne JH. More than synaptic plasticity: role of non-synaptic plasticity in learning and memory. Trends Neurosci 2010;33:17.
[74] Debanne D, Poo MM. Spike-timing dependent plasticity beyond synapse - pre- and post-synaptic plasticity of intrinsic neuronal excitability. Front Synaptic Neurosci 2010;2:21.
[75] Conforto AB, Nascimento-Farias da Guarda S. Transcranial Magnetic Stimulation. In: Ovbiagele B, editor. Ischemic Stroke Therapeutics. Springer; 2016. p 235–248.
[76] Daskalakis ZJ, Christensen BK, Fitzgerald PB, et al. Transcranial magnetic stimulation. J Neurol Neurosurg Psychiatr 2002;14:406–15.
[77] Xu Y, Hou Q, Russell SD. Neuroplasticity in post-stroke gait recovery and non-invasive brain stimulation. Neural Regener Res 2015;10:2072–80.
[78] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56.
[79] Matsuzaki M, Honkura N, Ellis-Davies GC, et al. Structural basis of long-term potentiation in single dendritic spines. Nature 2004;429:761–6.
[80] Cooke SF, Bliss TV. Plasticity in the human central nervous system. Brain 2006;129:1659–73.
[81] Gentner R, Wankerl K, Reinsberger C, et al. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity reversing meta-plasticity. Cereb Cortex 2008;18:2046–53.
[82] Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.
[83] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57:1899–901.
[84] Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged noninvasive modulation of brain excitability. Clin Neurophysiol 2003;114:589–95.
[85] Lefaucheur JP. Principles of therapeutic use of transcranial and epidural cortical stimulation. Clin Neurophysiol 2008;119:2179–84.
[86] Nitsche MA, Fricke K, Henschke U, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 2003;553:293–301.
[87] Mori F, Codeca C, Kusayanagi H, et al. Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis. Eur J Neurol 2010;17:295–300.
[88] Nielsen JF, Sinkjaer T, Jakobsen J. Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study. Multi Scler 1996;2:227–32.
[89] Wu D, Qian L, Zorowitz RD, et al. Effects on decreasing upper-limb post-stroke muscle tone using transcranial direct current stimulation: a Randomized Sham-Controlled Study. Arch Phys Med Rehabil 2013;94:1–8.
[90] Centonze D, Koch G, Versace V, et al. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology 2007;68:1045–50.
[91] Palm U, Ayache SS, Padberg F, et al. Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimul. 2014;7(6):849–54.
[92] Mori F, Ljoka C, Magni E, et al. Transcranial magnetic stimulation primes the effects of exercise therapy in multiple sclerosis. J Neurol 2011;258:1281–7.
[93] Kumru H, Murillo N, Samso JV, et al. Reduction of spasticity with repetitive transcranial magnetic stimulation in patients with spinal cord injury. Neurorehabil Neural Repair 2010;24:435–41.
[94] Kumru H, Benito J, Murillo N, et al. Effects of high-frequency repetitive transcranial magnetic stimulation on motor and gait improvement in incomplete spinal cord injury patients. Neurorehabil Neural Repair 2013;27:421–9.
[95] Tazoe T, Perez MA. Effects of repetitive transcranial magnetic stimulation on recovery of function after spinal cord injury. Arch Phys Med Rehabil 2015;96 (4 Suppl.):S145–55.
[96] Valle AC, Dionisio K, Pitskel NB, et al. Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. Dev Med Child Neurol 2007;49:534–8.
[97] Gupta M, Lal Rajak B, Bhatia D, et al. Effect of r-TMS over standard therapy in decreasing muscle tone of spastic cerebral palsy patients. J Med Eng Technol 2016;40(4):210–6.
[98] Gunduz A, Kumru H, Pascual-Leone A. Outcomes in spasticity after repetitive transcranial magnetic and transcranial direct current stimulations. Neural Regen Res 2014;9:712–8.
[99] Mally J, Dinya E. Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS). Brain Res Bull 2008;76:388–95.
[100] Kakuda W, Abo M, Kobayashi K, et al. Antispastic effect of low-frequency rTMS applied with occupational therapy in post-stroke patients with upper limb hemiparesis. Brain Inj 2011;25:496–502.
[101] Kakuda W, Abo M, Momosaki R, et al. Combined therapeutic application of botulinum toxin type A low-frequency rTMS, and intensive occupational therapy for post-stroke spastic upper limb hemiparesis. Eur J Phys Rehabil Med 2012;48:47–55.
[102] Yamada N, Kakuda W, Kondo T, et al. Bi-hemispheric repetitive transcranial magnetic stimulation combined with intensive occupational therapy for upper limb hemiparesis after stroke: a preliminary study. Int J Rehabil Res 2013;36:323–9.
[103] Theilig S, Podubecka J, Bosl K, et al. Functional neuromuscular stimulation to improve severe hand dysfunction after stroke: does inhibitory rTMS enhance therapeutic efficiency? Exp Neurol 2011;230:149–55.
[104] Wupuer S, Yamamoto T, Katayama Y, et al. F-wave suppression induced by supra-threshold high-frequency repetitive transcranial magnetic stimulation in post-stroke patients with increased spasticity. Neuromodulation 2013;16:206–11.
[105] Kakuda W, Abo M, Kobayashi K, et al. Low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy for post-stroke patients with upper limb hemiparesis: preliminary study of a 15-day protocol. Int J Rehabil Res. 2010;33:339–45.
[106] Kakuda W, Abo M, Kobayashi K, et al. Combination treatment of low-frequency rTMS and occupational therapy with levodopa administration: an intensive neurorehabilitative approach for upper limb hemiparesis after stroke. Int J Neurosci 2011;121:373–8.
[107] Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. Front Neural Circuits 2016;27(10):56.
[108] Etoh S, Noma T, Ikeda K, et al. Effects of repetitive trascranial magnetic stimulation on repetitive facilitation exercises of the hemiplegic hand in chronic stroke patients. J Rehabil Med 2013;45:843–7.
[109] Rastgoo M, Naghdi S, Nakhostin Ansari N, et al. Effects of repetitive transcranial magnetic stimulation on lower extremity spasticity and motor function in stroke patients. Disabil Rehabil 2016;38(19):1918–26.
[110] Barros Galvão SC, Borba Costa dos Santos R, Borba dos Santos P, et al. Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. Phys Med Rehabil 2014;95(2):222–9.
[111] Naghdi S, Ansari NN, Rastgoo M, et al. A pilot study on the effects of low frequency repetitive transcranial magnetic stimulation on mlower extremity spasticity and motor neuron excitability in patients after stroke. Bodyw Mov Ther 2015;19(4):616–23.
[112] Iodice R, Dubbioso R, Ruggiero L, et al. Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis. Restor Neurol Neurosci 2015;33(4):487–92.
[113] Aree-uea B, Auvichayapat N, Janyacharoen T, et al. Reduction of spasticity in cerebral palsy by anodal transcranial direct current stimulation. J Med Assoc Thai 2014;97:954–62.
[114] Vandermeeren Y, Lefebvre S, Desfontaines P, et al. Could dual-hemisphere transcranial direct current stimulation (tDCS) reduce spasticity after stroke? Acta Neurol Belg 2013;113(1):87–9.
[115] Ochi M, Saeki S, Oda T, et al. Effects of anodal and cathodal transcranial direct current stimulation combined with robotic therapy on severely affected arms in chronic stroke patients. J Rehabil Med 2013;45:137–40.
[116] Elsner B, Kugler J, Pohl M, et al. Transcranial direct current stimulation for improving spasticity after stroke: a systematic review with meta-analysis. J Rehabil Med 2016;48(7):565–70.
[117] Bradnam LV, Stinear CM, Barber PA, et al. Contra-lesional hemisphere control of the proximal paretic upper limb following stroke. Cereb Cortex 2012;22:2662–71.
[118] Krewer C, Hartl S, Müller F, et al. Effects of repetitive peripheral magnetic stimulation on upper-limb spasticity and impairment in patients with spastic

hemiparesis: a randomized, double-blind, sham-controlled study. Arch Phys Med Rehabil 2014;95:1039–47.
[119] Hubli M, Dietz V, Schrafl-Altermatt M, et al. Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. Clin Neurophysiol 2013;124:1187–95.
[120] Grey MJ, Klinge K, Crone C, et al. Post-activation depression of soleus stretch reflexes in healthy and spastic humans. Exp Brain Res 2008;185:189–97.
[121] Flamand VH, Beaulieu LD, Nadeau L, et al. Peripheral magnetic stimulation to decrease spasticity in cerebral palsy. Pediatr Neurol 2012;47(5):345–8.
[122] Krause P, Edrich T, Straube A. Lumbar repetitive magnetic stimulation reduces spastic tone increase of the lower limbs. Spinal Cord 2004;42 (2):67–72.
[123] Deyo RA, Walsh NE, Martin DC, et al. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. New Engl J Med 1990;322(23):1627–34.
[124] Mills PB, Dossa F. Transcutaneous electrical nerve stimulation for management of limb spasticity: a systematic review. J Phys Med Rehabil 2016;95(4):309–18.
[125] Lappin MS, Lawrie FW, Richards TL, et al. Effects of a pulsed electromagnetic therapy on multiple sclerosis fatigue and quality of life: a double-blind, placebo controlled trial. Altern Ther Health Med 2003;9:38–48.
[126] Miller L, Mattison P, Paul L, et al. The effects of Transcutaneous Electrical Nerve Stimulation (TENS) on spasticity in Multiple Sclerosis. Multi Scler 2007;13:527–33.
[127] Ng SS, Hui-Chan CW. Does the use of TENS increase the effectiveness of exercise for improving walking after stroke? A randomized controlled clinical trial. Clin Rehabil 2009;23:1093103.
[128] Knutson JS, Harley MY, Hisel TZ, et al. Contralaterally controlled functional electrical stimulation for stroke rehabilitation. Conf Proc IEEE Eng Med Biol Soc 2012;2012:314–7.
[129] Harvey LA, Glinsky JV, Bowden JL. The effectiveness of 22 commonly administered physiotherapy interventions for people with spinal cord injury: a systematic review. Spinal cord 2016.
[130] Oo WM. Efficacy of addition of transcutaneous electrical nerve stimulation to standardized physical therapy in subacute spinal spasticity: a randomized controlled trial. Arch Phys Med Rehabil 2014;95(11):2013–20.
[131] Jordan N. Managing early multiple sclerosis. Practitioner 1998;242 (1586):400–4132.
[132] Alabdulwahab SS, Al-Gabbani M. Transcutaneous electrical nerve stimulation of hip adductors improves gait parameters of children with spastic diplegic cerebral palsy. NeuroRehabilitation 2010;26:115–22.
[133] Levin MF, Hui-Chan CW. Relief of hemiparetic spasticity by TENS is associated with improvement in reflex and voluntary motor functions. Electroencephalogr Clin Neurophysiol 1992;85:131–42.
[134] Armutlu K, Meriç A, Kirdi N, et al. The effect of transcutaneous electrical nerve stimulation on spasticity in multiple sclerosis patients: a pilot study. Neurorehabil Neural Repair 2003;17:79–82.
[135] Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. Yale J Biol Med 2012;85:201–15.
[136] Stein C, Fritsch CG, Robinson C, et al. Effects of electrical stimulation in spastic muscles after stroke: systematic review and meta-analysis of randomized controlled trials. Stroke 2015;46:2197–205.
[137] Chen SC, Chen YL, Chen CJ, et al. Effects of surface electrical stimulation on the muscle-tendon junction of spastic gastrocnemius in stroke patients. Disabil Rehabil 2005;27:105–10.
[138] Dewald JP, Given JD, Rymer WZ. Long-lasting reductions of spasticity induced by skin electrical stimulation. IEEE Trans Rehabil Eng 1996;4:231–42.
[139] Wang RY, Tsai MW, Chan RC. Effects of surface spinal cord stimulation on spasticity and quantitative assessment of muscle tone in hemiplegic patients. Am J Phys Med Rehabil 1998;77:282–7.
[140] Bakhtiary AH, Fatemy E. Does electrical stimulation reduce spasticity after stroke? A randomized controlled study. Clin Rehabil 2008;22:418–25.
[141] Kamper DG, Yasukawa AM, Barrett KM, et al. Effects of neuromuscular electrical stimulation treatment of cerebral palsy on potential impairment mechanisms: a pilot study. Pediatr Phys Ther 2006;18:31–8.
[142] Vanderthommen M, Duchateau J. Electrical stimulation as a modality to improve performance of the neuromuscular system. Exerc Sport Sci Rev 2007;35:180–5.
[143] Sabut SK, Sikdar C, Kumar R, et al. Functional electrical stimulation of dorsiflexor muscle: effects on dorsiflexor strength, plantarflexor spasticity, and motor recovery in stroke patients. NeuroRehabilitation 2011;29:393–400.
[144] Sahin N, Ugurlu H, Albayrak I. The efficacy of electrical stimulation in reducing the post-stroke spasticity: a randomized controlled study. Disabil Rehabil 2012;34:151.
[145] Van der Salm A, Veltink PH, Ijzerman MJ, et al. Comparison of electric stimulation methods for reduction of triceps surae spasticity in spinal cord injury. Arch Phys Med Rehabil 2006;87:222–8.
[146] Mirbagheri MM, Ladouceur M, Barbeau H. The effects of long-term FES-assisted walking on intrinsic and reflex dynamic stiffness in spastic spinal-cord-injured subjects. IEEE Trans Neural Syst Rehabil Eng 2002;10:280–9.
[147] Carpentier A, Duchateau J, Hainaut K. Motor unit behavior and contractile changes during fatigue in the human first dorsal interosseus. J Physiol 2001;534:903–12.
[148] Denegar C, Saliba E, Saliba S, et al. Therapeutic modalities for musculoskeletal injuries. In: Champaign IL, editor. Human Kinetics; 2009. p. 105–128.
[149] Knutson JS, Harley MY, Hisel TZ, et al. Improving hand function in stroke survivors: a pilot study of contralaterally controlled functional electric stimulation in chronic hemiplegia. Arch Phys Med Rehabil 2007;88:513–20.
[150] Kesar TM, Perumal R, Jancosko A, et al. Novel patterns of functional electrical stimulation have an immediate effect on dorsiflexor muscle function during gait for people poststroke. Phys Ther 2010;90:55–66.
[151] Ambrosini E, Ferrante S, Pedrocchi A, et al. Cycling induced by electrical stimulation improves motor recovery in post-acute hemiparetic patients. Stroke 2011;42:1068–73.
[152] Yeh CY, Tsai KH, Su FC, et al. Effect of a bout of leg cycling with electrical stimulation on reduction of hypertonia in patients with stroke. Arch Phys Med Rehabil 2010;91:1731–6.
[153] Griffin L, Decker M, Hwang J, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. J Electromyogr Kinesiol 2009;19:614–22.
[154] Hardy K, Suever K, Sprague A, et al. Combined bracing, electrical stimulation, and functional practice for chronic, upper-extremity spasticity. Am J Occup Ther 2010;64:720–6.
[155] Popovic DB, Sinkaer T, Popovic MB. Electrical stimulation as a means for achieving recovery of function in stroke patients. NeuroRehabilitation 2009;25:45–58.
[156] Lo HC, Tsai KH, Su FC, et al. Effects of a functional electrical stimulation-assisted leg-cycling wheelchair on reducing spasticity of patients after stroke. J Rehabil Med 2009;41:242–6.
[157] Wang YH, Meng F, Zhang Y, et al. Full-movement neuromuscular electrical stimulation improves plantar flexor spasticity and ankle active dorsiflexion in stroke patients: a randomized controlled study. Clin Rehabil 2016;30 (6):577–86.
[158] Yıldıcczgören MT, Nakipoğlu Yüzer GF, Ekiz T, et al. Effects of neuromuscular electrical stimulation on the wrist and finger flexor spasticity and hand functions in cerebral palsy. Pediatr Neurol. 201;51(3):360-4
[159] Ozer K, Chesher SP, Scheker LR. Neuromuscular electrical stimulation and dynamic bracing for the management of upper-extremity spasticity in children with cerebral palsy. Dev Med Child Neurol 2006;48(7):559–63.
[160] Scheker LR, Chesher SP, Ramirez S. Neuromuscular electrical stimulation and dynamic bracing as a treatment for upper-extremity spasticity in children with cerebral palsy. J Hand Surg Br 1999;24(2):226–32.
[161] Johnston TE, Wainwright SF. Cycling with functional electrical stimulation in an adult with spastic diplegic cerebral palsy. Phys Ther 2011;91(6):970–82.
[162] Ho CH, Triolo RJ, Elias AL, et al. Functional electrical stimulation and spinal cord injury. Phys Med Rehabil Clin N Am 2014;25(3):631–54.
[163] Lo HC, Hsu YC, Hsueh YH, et al. Cycling exercise with functional electrical stimulation improves postural control in stroke patients. Gait Posture 2012;35(3):506–10.
[164] Lee YY, Lin KC, Cheng HJ, et al. Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial. J Neuroeng Rehabil 2015;12:96.
[165] Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. Neuromodulation 2014;17:242–54.
[166] Lorenzen C, Maschette W, Koh M, et al. Inconsistent use of terminology in whole body vibration exercise research. J Sci Med Sport 2009;12(6):676–8.
[167] Nordlund MM, Thorstensson A. Strength training effects of whole-body vibration? Scand J Med Sci Sports 2007;17:12–7.
[168] Cardinale M, Bosco C. The use of vibration as an exercise intervention. Exerc Sport Sci Rev 2003;31:3–7.
[169] Cochrane DJ, Stannard SR, Sargeant AJ, et al. The rate of muscle temperature increase during acute whole-body vibration exercise. Eur J Appl Physiol 2008;103:441–8.
[170] Lohman EB, 3rd, Petrofsky JS, Maloney-Hinds C, et al. The effect of whole body vibration on lower extremity skin blood flow in normal subjects. Med Sci Monit. 2007;13:CR71–76.
[171] Cardinale M, Soiza RL, Leiper JB, et al. Hormonal responses to a single session of whole body vibration exercise in elderly individuals. Br J Sports Med 2010;44(4):284–8.
[172] Liao LR, Ng GY, Jones AY, et al. Whole-body vibration intensities in chronic stroke: a randomized controlled trial. Med Sci Sports Exerc 2016;48 (7):1227–38.
[173] Huang M, Liao LR, Pang MY. Effects of whole body vibration on muscle spasticity for people with central nervous system disorders: a systematic review. Clin Rehabil 2015;11:pii 0269215515621117.
[174] Schyns F, Paul L, Finlay K, et al. Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functional performance. Clin Rehabil 2009;23(9):771–81.
[175] Park SY, Son WM, Kwon OS. Effects of whole body vibration training on body composition, skeletal muscle strength, and cardiovascular health. J Exerc Rehabil 2015;11(6):289–95.
[176] Kantele S, Karinkanta S, Sievänen H. Effects of long-term whole-body vibration training on mobility in patients with multiple sclerosis: a meta-analysis of randomized controlled trials. J Neurol Sci. 2015;358(1–2):31–7.
[177] Cheng HY, Ju YY, Chen CL, et al. Effects of whole body vibration on spasticity and lower extremity function in children with cerebral palsy. Hum Mov Sci 2015;39:65–72.
[178] Tupimai T, Peungsuwan P, Prasertnoo J, et al. Effect of combining passive muscle stretching and whole body vibration on spasticity and physical

performance of children and adolescents with cerebral palsy. J Phys Ther Sci 2016;28(1):7–13.
[179] Douquette SA, Giuliano AM, Starmer DJ. Whole body vibration and cerebral palsy: a systematic review. J Can Chiropr Assoc 2015;59:245–52.
[180] Kang J, Porfido T, Ismaili C, et al. Metabolic responses to whole-body vibration: effect of frequency and amplitude. Eur J Appl Physiol 2016;116 (9):1829–39.
[181] Castillo-Bueno I, Ramos-Campo DJ, Rubio-Arias JA. Effects of whole-body vibration training in patients with multiple sclerosis: a systematic review. Neurologia. 2016. pii: S0213–4853(16)30066–4.
[182] Ness LL, Field-Fote EC. Effect of whole-body vibration on quadriceps spasticity in individuals with spastic hypertonia due to spinal cord injury. Restor Neurol Neurosci 2009;27:621–31.
[183] Ahlborg L, Andersson C, Julin P. Whole-body vibration training compared with resistance training: effect on spasticity, muscle strength and motor performance in adults with cerebral palsy. J Rehabil Med 2006;38:302–8.
[184] Murillo N, Kumru H, Vidal-Samso J, et al. Decrease of spasticity with muscle vibration in patients with spinal cord injury. Clin Neurophysiol 2011;122 (6):1183–9.
[185] Noma T, Matsumoto S, Etoh S, et al. Anti-spastic effects of the direct application of vibratory stimuli to the spastic muscles of hemiplegic limbs in post-stroke patients. Brain Inj 2009;23:623–31.
[186] Sadeghi M1, Sawatzky B. Effects of vibration on spasticity in individuals with spinal cord injury: a scoping systematic review. Am J Phys Med 2014;93:995–1007.
[187] Caliandro P, Celletti C, Padua L, et al. Focal muscle vibration in the treatment of upper limb spasticity: a pilot randomized controlled trial in patients with chronic stroke. Arch Phys Med Rehabil 2012;93:1656–61.
[188] Casale R, Damiani C, Maestri R, et al. Localized 100 Hz vibration improves function and reduces upper limb spasticity: a double-blind controlled study. Eur J Phys Rehabil Med 2014 Oct;50:495–504.
[189] Tavernese E, Paoloni M, Mangone M, et al. Segmental muscle vibration improves reaching movement in patients with chronic stroke. A randomized controlled trial. NeuroRehabilitation 2013;32:591–9.
[190] Paoloni M, Tavernese E, Fini M, et al. Segmental muscle vibration modifies muscle activation during reaching in chronic stroke: a pilot study. NeuroRehabilitation 2014;35:405–14.
[191] Murillo N, Valls-Sole J, Vidal J, et al. Focal vibration in neurorehabilitation. Eur J Phys Rehabil Med 2014;50:231–42.
[192] Rodríguez Jiménez S, Benítez A, García González MA. Effect of vibration frequency on agonist and antagonist arm muscle activity. Eur J Appl Physiol 2015;115:1305–12.
[193] Rosenkranz K, Rothwell JC. Differential effect of muscle vibration on intracortical inhibitory circuits in humans. J Physiol 2003;551:649–60.
[194] Colebatch JG, Gandevia SC. The distribution of muscular weakness in upper motor neuron lesions affecting the arm. Brain 1989;112:749–63.
[195] Sukal-Moulton T, Krosschell KJ, Gaebler-Spira DJ. Motor impairment factors related to brain injury timing in early hemiparesis. Part I: expression of upper-extremity weakness. Neurorehabil Neural Repair 2014;28:13–23.
[196] Twitchell TE. The restoration of motor function following hemiplegia in man. Brain 1951;74:443–80.
[197] Brunnstrom S. Movement therapy in hemiplegia: a neurophysiological approach. New York: Harper & Row; 1970.
[198] Zackowski KM, Dromerick AW, Sahrmann SA. How do strength, sensation, spasticity and joint individuation relate to the reaching deficits of people with chronic hemiparesis? Brain 2004;127:1035–46.
[199] Ashby P, Verrier M, Lightfoot E. Segmental reflex pathways in spinal shock and spinal spasticity in man. J Neurol Neurosurg Psychiatry 1974;37 (12):1352–60.
[200] Roll JP, Vedel JP, Ribot E. Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. Exp Brain Res 1989;76 (1):213–22.
[201] Dindar F, Verrier M. Studies on the receptor responsible for vibration induced inhibition of monosynaptic reflexes in man. J Neurol Neurosurg Psychiatry 1975;38(2):155–60.
[202] Seo HG, Oh BM, Leigh JH, et al. Effect of Focal Muscle Vibration on Calf Muscle Spasticity: a Proof-of-Concept Study.PM R. 2016;16: S1934–1482.
[203] Spina E, Carotenuto A, Aceto MG, et al. The effects of mechanical focal vibration on walking impairment in multiple sclerosis patients: a randomized, double-blinded vs placebo study. Restor Neurol Neurosci 2016.
[204] Alfonsi E, Paone P, Tassorelli C, et al. Acute effects of high-frequency microfocal vibratory stimulation on the H reflex of the soleus muscle. A double-blind study in healthy subjects. Funct Neurol. 2015;30(4):269–74.
[205] Saggini R, Bellomo RG. Integration to focal vibration in neurorehabilitation. Eur J Phys Rehabil Med 2015;51(4):508.
[206] Liepert J, Binder C. Vibration-induced effects in stroke patients with spastic hemiparesis—a pilot study. Restor Neurol Neurosci 2010;28(6):729–35.
[207] Kawahira K, Higashihara K, Matsumoto S, et al. New functional vibratory stimulation device for extremities in patients with stroke. Int J Rehabil Res 2004;27(4):335–7.
[208] Casale R. Focal, local or segmental vibration? Eur J Phys Rehabil Med 2015;51 (4):507–8.
[209] Lance JW. The control of muscle tone, reflexes, and movement: robert Wartenberg lecture. Neurology 1980;30:1303–13.
[210] Mottram CJ, Suresh NL, Heckman CJ. Origins of abnormal excitability in biceps brachii motoneurons of spastic-paretic stroke survivors. J Neurophysiol 2009;102:2026–38.
[211] Gracies JM. Pathophysiology of spastic paresis. ii: emergence of muscle overactivity. Muscle Nerve 2005;31:552–71.
[212] Van Kuijk AA, Pasman JW, Hendricks HT. Predicting hand motor recovery in severe stroke: the role of motor evoked potentials in relation to early clinical assessment. Neurorehabil Neural Repair 2009;23:45–51.
[213] Butefisch C, Hummelsheim H, Denzler P. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. J Neurol Sci 1995;130:59–68.
[214] Wolf SL, Winstein CJ, Miller JP. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 2006;296:2095–104.
[215] Moreau NG, Bodkin AW, Bjornson K, et al. Effectiveness of rehabilitation interventions to improve gait speed in children with cerebral palsy: systematic review and meta-analysis. Phys Ther 2016.
[216] Celletti C, Camerota F. Preliminary evidence of focal muscle vibration effects on spasticity due to cerebral palsy in a small sample of Italian children. Clin Ter 2011;162(5):e125–8.
[217] Abdel Gawad HA, Abdel Karim AE, Mohammed AH. Shock wave therapy for spastic plantar flexor muscles in hemiplegic cerebral palsy children. Egypt J Med Hum Genet 2015;16:269–75.
[218] Manganotti P, Amelio E. Long-term effect of shock wave therapy on upper limb hypertonia in patients affected by stroke. Stroke 2005;36:1967–71.
[219] Rompe JD, Burger R, Hopf C, et al. Shoulder function after extracorporeal shock wave therapy for calcific tendinitis. J Shoulder Elbow Surg 1998;7:505–9.
[220] Wang CJ, Huang HY, Pai CH. Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg 2002;41:16–22.
[221] Ciampa AR, de Prati AC, Amelio E, et al. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett, 2005;579:6839–45.
[222] Zhang X, Yan X, Wang C, et al. The dose-effect relationship in extracorporeal shock wave therapy: the optimal parameter for extracorporeal shock wave therapy. J Surg Res 2014;186:484–92.
[223] Mariotto S, Cavalieri E, Amelio E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide 2005;12:89–96.
[224] Loew M, Deacke W, Kusnierczak D, et al. Shock-wave therapy is effective for chronic calcifying tendinitis of the shoulder. Bone Joint J 1999;81:863–7.
[225] Siebrt W, Buch M. Extracorporeal shock wave in orthopaedics. Berlin, Heidelberg: Springer-Verlag; 1998.
[226] Valchanov VD, Michailov P. High energy shock waves in the treatment of delayed and nonunion of fractures. Internat Orthop 1991;15:181–4.
[227] Rompe JD, Hopf C, Kullmer K, et al. Analgesic effect of ESWT on chronic tennis elbow. Bone Joint J 1996;78:233–7.
[228] Rompe JD, Decking J, Schoellner C, et al. Shock wave application for chronic plantar fascitis in running athletes: a prospective, randomized, placebo-controlled trial. Am J Sports Med 2003;31:68–75.
[229] Li TY, Chang CY, Chou YC, et al. Effect of radial shock wave therapy on spasticity of the upper limb in patients with chronic stroke: a prospective, randomized, single blind, controlled trial. Medicine (Baltimore) 2016;95(18): e3544.
[230] Moon SW, Kim JH, Jung MJ, et al. The effect of extracorporeal shock wave therapy on lower limb spasticity in subacute stroke patients. Ann Rehabil Med 2013;37(4):461–70.
[231] Sohn MK, Cho KH, Kim Y, et al. Spasticity and electrophysiologic changes after extracorporeal shock wave therapy on gastrocnemius. Ann Phys Rehabil Med 2011;35(5):599–604.
[232] Gonkova MI, Ilieva EM, Ferriero G, et al. Effect of radial shock wave therapy on muscle spasticity in children with cerebral palsy. Int J Rehabil Res 2013;36 (3):284–90.
[233] Amelio E, Manganotti P. Effect of shock wave stimulation on hypertonic plantar flexor muscles in patients with cerebral palsy: a placebo-controlled study. J Rehabil Med 2010;42(4):339–43.
[234] Ansari NN, Adelmanesh F, Naghdi S, et al. The effect of physiotherapeutic ultrasound on muscle spasticity in patients with hemiplegia: a pilot study. Electromyogr Clin Neurophysiol 2006;46:247–52.
[235] Ansari NN, Naghdi S, Bagheri H, et al. Therapeutic ultrasound in the treatment of ankle plantarflexor spasticity in a unilateral stroke population: a randomized, single-blind, placebo-controlled trial. Electromyogr Clin Neurophysiol 2007;47:137–43.
[236] Sahin N, Ugurlu H, Karahan AY. Efficacy of therapeutic ultrasound in the treatment of spasticity: a randomized controlled study. NeuroRehabilitation 2011;29:61–6.
[237] Rahman MS, Uddin MT. Comparative efficacy of pregabalin and therapeutic ultrasound versus therapeutic ultrasound alone on patients with post stroke shoulder pain. Mymensingh Med J 2014;23(3):456–60.
[238] Santamato A, Micello MF, Panza F, et al. Extracorporeal shock wave therapy for the treatment of poststroke plantar-flexor muscles spasticity: a prospective open-label study. Top Stroke Rehabil 2014;21(Suppl. 1):S17–24.
[239] Ansari NN, Naghdi S, Hasson S, et al. Efficacy of therapeutic ultrasound and infrared in the management of muscle spasticity. Brain Inj 2009;23:632–8.

[240] Picelli A, Dambruoso F, Bronzato M, et al. Efficacy of therapeutic ultrasound and transcutaneous electrical nerve stimulation compared with botulinum toxin type A in the treatment of spastic equinus in adults with chronic stroke: a pilot randomized controlled trial. Top Stroke Rehabil 2014;21:S8–16.
[241] Harlaar J, Ten Kate JJ, Prevo AJ, et al. The effect of cooling on muscle co-ordination in spasticity: assessment with the repetitive movement test. Disabil Rehabil 2001;23:453–61.
[242] Lee SU, Bang MS, Han TR. Effect of cold air therapy in relieving spasticity: applied to spinalized rabbits. Spinal Cord 2002;40:167–73.
[243] Cardenas DD, Dalal K. Spinal cord injury rehabilitation. Phys Med Rehabil Clin N Am 2014;25(3):15–6.
[244] Krukowska J, Dalewski M, Czernicki J. Evaluation of effectiveness of local cryotherapy in patients with post-stroke spasticity. Wiad Lek 2014;67(2 Pt 1):71–5.
[245] Mecomber SA, Herman RM. Effects of local hypothermia on reflex and voluntary activity. Phys Ther 1971;51(3):271–81.
[246] Kesiktas N, Paker N, Erdogan N, et al. The use of hydrotherapy for the management of spasticity. Neurorehabil Neural Repair 2004;18(4):268–73.
[247] Erceg-Rukavina T, Stefanovski M. Balneotherapy in treatment of spastic upper limb after stroke. Med Arch 2015;69(1):31–3.
[248] Matsumoto S, Kawahira K, Etoh S, et al. Short-term effects of thermotherapy for spasticity on tibial nerve F-waves in post-stroke patients. Int J Biometeorol 2006;50:243–50.
[249] Lee GP, Ng GY. Effects of stretching and heat treatment on hamstring extensibility in children with severe mental retardation and hypertonia. Clin Rehabil 2008;22:771–9.
[250] Galea MP. Physical modalities in the treatment of neurological dysfunction. Clin Neurol Neurosurg 2012;114:483–8.
[251] Nakhostin Ansari N, Naghdi S, Hasson S, et al. Efficacy of therapeutic ultrasound and infrared in the management of muscle spasticity. Brain Inj 2009;23:632–8.
[252] Tepperman PS, Devlin M. Therapeutic heat and cold. A practitioner's guide. Postgrad Med 1983;73(1):69–76.
[253] Krebs HI, Hogan N. Robotic therapy: the tipping point. Am J Phys Med Rehabil 2012;91(11 Suppl. 3):S290–7.
[254] Rosati G, Gallina P, Masiero S. Design, implementation and clinical tests of a wire-based robot for neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng 2007;15:560–9.
[255] Posteraro F, Mazzoleni S, Aliboni S, et al. Upper limb spasticity reduction following active training: a robot-mediated study in patients with chronic hemiparesis. J Rehabil Med 2010;42:279–81.
[256] Hi Krebs, Mernoff S, Fasoli Se, et al. A comparison of functional and impairment-based robotic training in severe to moderate chronic stroke: a pilot study. Neurorehabilitation 2008;23:81–7.
[257] Fazekas G, Horvath M, Troznai T, et al. Robot-mediated upper limb physiotherapy for patients with spastic hemiparesis: a preliminary study. J Rehabil Med 2007;39:580–2.
[258] Chang WH, Kim YH. Robot-assisted therapy in stroke rehabilitation. J Stroke 2013;15:174–81.
[259] Di Pino G, Pellegrino G, Assenza G, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. Nat Rev Neurol 2014;10:597–608.
[260] Beom J, Koh S, Nam HS, et al. Robotic Mirror Therapy System for Functional Recovery of Hemiplegic Arms. J Vis Exp. 2016;(114).
[261] Toth A, Fazekas G, Arz G, et al. Passive Robotic Movement Therapy of the Spastic Hemiparetic Arm with REHAROB: report of the First Clinical Test and the Followup System Improvement. Rehabilitation Robotics, 2005.
[262] Ghiasi F, Hadian MR, Bagheri H, et al. Change of spasticity following robotic-assisted gait training in patients with chronic incomplete spinal cord injury: preliminary results. IEEE Int Conf Rehabil Robot 2011;2011:5975443.
[263] Mirbagheri MM, Ness LL, Patel C, et al. The effects of robotic-assisted locomotor training on spasticity and volitional control. IEEE Int Conf Rehabil Robot 2011;2011:5975443.
[264] Pennati GV, Da Re C, Messineo I, et al. How could robotic training and botolinum toxin be combined in chronic post stroke upper limb spasticity? A pilot study. Eur J Phys Rehabil Med 2015;51(4):381–7.
[265] Grimm F, Walter A, Spüler M, et al. Hybrid neuroprosthesis for the upper limb: combining brain-controlled neuromuscular stimulation with a multi-joint arm exoskeleton. Front Neurosci 2016;9(10):367.
[266] Duffell LD, Brown GL, Mirbagheri MM. Facilitatory effects of anti-spastic medication on robotic locomotor training in people with chronic incomplete spinal cord injury. J Neuroeng Rehabil 2015;12:29.
[267] Torricelli D, Gonzalez J, Weckx M, et al. Human-like compliant locomotion: state of the art of robotic implementations. Bioinspir Biomim 2016;11 (5):051002.
[268] Calabrò RS, Cacciola A, Bertè F, et al. Robotic gait rehabilitation and substitution devices in neurological disorders: where are we now? Neurol Sci 2016;37(4):503–14.
[269] Burgar CG, Lum PS, Scremin AM, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. J Rehabil Res Dev 2011;48(4):445–58.
[270] Cortes M, Elder J, Rykman A, et al. Improved motor performance in chronic spinal cord injury following upper-limb robotic training. NeuroRehabilitation 2013;33(1):57–65.
[271] Dundar U, Toktas H, Solak O, et al. A comparative study of conventional physiotherapy versus robotic training combined with physiotherapy in patients with stroke. Top Stroke Rehabil 2014;21(6):453–61.
[272] Vaney C, Gattlen B, Lugon-Moulin V, et al. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. Neurorehabil Neural Repair 2012;26 (3):212–21.
[273] Straudi S, Benedetti MG, Venturini E, et al. Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. NeuroRehabilitation 2013;33(4):555–63.
[274] Sale P, Lombardi V, Franceschini M. Hand robotics rehabilitation: feasibility and preliminary results of a robotic treatment in patients with hemiparesis. Stroke Res Treat 2012;2012:820931.
[275] Picelli A, Chemello E, Castellazzi P, et al. Combined effects of transcranial direct current stimulation (tDCS) and transcutaneous spinal direct current stimulation (tsDCS) on robot-assisted gait training in patients with chronic stroke: a pilot, double blind, randomized controlled trial. Restor Neurol Neurosci 2015;33:357–68.
[276] Middleton A, Fritz SL, Liuzzo DM, et al. Using clinical and robotic assessment tools to examine the feasibility of pairing tDCS with upper extremity physical therapy in patients with stroke and TBI: a consideration-of-concept pilot study. Neurorehabilitation 2014;35:741–54.
[277] Giacobbe V, Krebs HI, Volpe BT, et al. Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: the dimension of timing. Neurorehabilitation 2013;33(1):49–56.
[278] Smania N, Picelli A, Munari D, et al. Rehabilitation procedures in the management of spasticity. Eur J Phys Rehabil Med 2010;46(3):423–38.
[279] Massie CL, Kantak SS, Narayanan P, et al. Timing of motor cortical stimulation during planar robotic training differentially impacts neuroplasticity in older adults. Clin Neurophysiol 2015;126:1024–32.
[280] Aprile I, Di Sipio E, Germanotta M, et al. Muscle focal vibration in healthy subjects: evaluation of the effects on upper limb motor performance measured using a robotic device. Eur J Appl Physiol 2016;116(4):729–37.
[281] Avanzino L, Pelosin E, Abbruzzese G, et al. Shaping motor cortex plasticity through proprioception. Cereb Cortex 2014;24:2807–14.
[282] Cotey D, Hornby TG, Gordon KE, et al. Increases in muscle activity produced by vibration of the thigh muscles during locomotion in chronic human spinal cord injury. Exp Brain Res 2009;196:361–74.
[283] Cassidy JM, Gillick BT, Carey JR. Priming the brain to capitalize on metaplasticity in stroke rehabilitation. Phys Ther 2014;94:139–50.
[284] Hulme SR, Jones OD, Raymond CR, et al. Mechanisms of heterosynaptic metaplasticity. Philos Trans R Soc Lond B Biol Sci 2013;369:20130148.
[285] Khan F, Turner-Stokes L, Ng L, et al. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database System Rev 2007;(2):CD006036.
[286] Gold R, Oreja-Guevara C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. Expert Rev Neurother 2013;13S:55–9.
[287] Atul T Patel. Early Diagnosis of Post-stroke Spasticity and Treatment Options. US Neurol. 2010;5:47–51.
[288] Francisco GE, McGuire JR. Post-stroke spasticity management. Stroke 2012;43:3132–6.
[289] Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. Front Hum Neurosci 2015;9:192.