Update on rehabilitation in multiple sclerosis

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Summary
Given that mobility impairment is a hallmark of multiple sclerosis, people with this disease are likely to benefit from rehabilitation therapy throughout the course of their illness. The review provides an update on rehabilitation focused on balance and walking impairment. Classical rehabilitation focusing on muscle rehabilitation, neurotherapeutic facilitation is effective and recommended. Other techniques did not prove their superiority: transcutaneous neurostimulation, repetitive magnetic stimulation, electromagnetic therapy, whole body vibration and robot-assisted gait rehabilitation and need more studies to conclude. Cooling therapy, hydrotherapy, orthoses and textured insoles could represent a complementary service to other techniques in specific conditions. Multidisciplinary rehabilitation program provides positive effects and high satisfaction for patients with multiple sclerosis but needs more evaluation. New technologies using serious game and telerehabilitation seem to be an interesting technique to promote physical activity, self-management and quality of life. Rehabilitation like other therapy needs regular clinical evaluation to adapt the program and propose appropriate techniques. Moreover, the objective of rehabilitation needs to be decided with the patient with realistic expectation.

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) that can affect a wide range of functions, including muscle strength, coordination, sensation, vision and cognition, inducing balance and mobility limitations [1]. Physical therapy (PT) provides interventions to maintain or improve balance, mobility, build exercises and activity tolerance, respiratory function and reduce impact of spasticity. Interventions are often focused on educating patients and family members [2]. Rehabilitation is part of the therapy of MS since its description in 1870 by J.M. Charcot [3]. In the 1950s, publications on this theme were common and mostly advised around the use of physical agents such as cold baths, electrotherapy, but also the practice of passive and active mobilization and physical exercise… [4–7]. Physical activity has been proposed for many years [8]. The first randomized controlled trial (RCT) was published in 1996 by Petajan et al. [9]. It concluded that physical activity induced no risk and that exercise training was effective in this pathology. After the 1990s, the emergence of new technologies: robotics, neuromodulation and more recently telerehabilitation (TR) provide alternative arrangements for implementing rehabilitation. The
effectiveness of rehabilitation has been widely studied but usually the level of evidence is low to moderate and presents poor methodology [10,11]. We can also notice that there are often many biases in randomization, low inhomogeneous samples, no double blind and lack of description of interventions [10,11]. The assessment of effects is also difficult to prove although some validated scales are available to analyse the effectiveness of the rehabilitation programs.

We propose through a literature review to update and study more specifically what is new in the rehabilitative approach of balance and mobility impairment in patient with MS (PwMS).

**What kinds of rehabilitation techniques are effective in MS?**

### Neurotherapeutics approaches

PT includes wide range of techniques and conceptual treatment methods that are not yet studied with rigorous scientific methods but, nevertheless, may be of value. Bobath concept, proprioceptive neuromuscular facilitation, Vojta reflex locomotion have already been used since the 1950s [12]. Their theoretical approaches were based on the motor control and are called facilitation approaches. A new model of motor control is the systems model [13] which forms the basis for the task-oriented therapeutic approach focusing on specific disabilities of an individual patient. These methods have in common the aim of improving activities of daily living (ADL) by applying internal and external stimuli to achieve better movement. In the task-oriented approach a patient learns by repeating a given specific task in different environments and under different conditions. The ability to carry out a specific task may be more important than the quality of the execution and leads to improve ADL [14,15].

Some authors evaluated the effect on balance of these approaches in PwMS and revealed a significant effect on the time one-leg stance test when outpatient physiotherapy and home exercises based on an individualized problem-solving approach were compared with no treatment [16,17]. Lord et al. [18] and Wiles et al. [19] have compared a facilitation approach with functional exercise and they both reported statistically unchanged performance on balance tested by Berg balance test (BBS) and timed one-leg stance test following the facilitation approach when compared with functional exercise. Bronson et al. [20] found that hippotherapy had a positive effect on balance in PwMS but this finding was based on only 3 non-RCT studies. Kanekar et al. [21] more recently proposed to use a light finger touch contact with a stationary surface to improve upright postural stability. Results showed that this technique was effective in reducing postural sway in both the sagittal and frontal planes, in all experimental conditions. Authors concluded that light finger touch contact is effective in enhance postural control in PwMS moderately disabled and can be considered as a useful rehabilitative strategy and an aid to stability [21].

These findings indicate small, but significant effects of neuro-rehabilitation approaches in PwMS who have mild to moderate level of disability. However, evidence for severely disabled people is lacking, and further research is needed.

### Exercise training

Exercise training has been proposed to counteract many symptoms of MS and their consequences on ADL [22-24]. Two types of exercises are proposed alone or combined: aerobic exercise training and resistance training programs.

#### Aerobic training program

The goal of aerobic training is to improve physical capacity and the indicators are represented by maximal oxygen uptake ($V_{O2\text{max}}$) and power output (mechanical power generated during exercise). Patients are asked to perform some exercises on different support like step, leg and arm cycling ergometers, walking, treadmill, aquatic exercises... Training programs must be realized at a minimum frequency of 2 to 3 times per week for 30 to 60 minutes at moderate intensities (60-80% maximum work rate or 60% $V_{O2\text{max}}$). These programs are effective in improving aerobic capacity and power output in MS [25].

#### Resistance training program

Their target is to increase muscular strength impact mobility, balance and performance of ADL [25]. Resistance training program use various types of machines (weight machines, free weights, resistance bands, locomotor training, cycling, and aquatics training). Resistance training is generally performed at an intensity of 10 to 12 repetitions maximum, 2 to 3 times per week during 8 to 20 weeks. Strong evidence suggests that

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**Glossary**

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<th>ADL</th>
<th>activity of daily living</th>
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<td>AFO</td>
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<td>BBS</td>
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<td>BWS</td>
<td>body weight support</td>
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<td>central nervous system</td>
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<td>expanded disability status scale</td>
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<td>MS</td>
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<td>nitric oxide</td>
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<td>PT</td>
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<td>PwMS</td>
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<td>QOL</td>
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<td>RAGT</td>
<td>robot-assisted gait training</td>
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<td>randomized controlled trial</td>
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<td>TENS</td>
<td>transcutaneous electrical nerve stimulation</td>
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<td>$V_{O2\text{max}}$</td>
<td>maximal oxygen uptake</td>
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<td>VR</td>
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exercise training improves muscular strength in MS [25]. Aerobic, resistance training or a combination of both may improve vitality, walking speed and endurance in PwMS [25].

**Conclusion**

Moderate-intensity training program performed 2 to 3 per week is effective in increasing aerobic and muscular strength among adults with mild to moderate disability resulting from MS. Exercise may be effective in enhancing mobility in PwMS [25]. Few studies have specially focused on MS patients with high level of disability (EDSS 6-7). Pilluti et al. [26] showed that treadmill training (TT) with body weight support resulted in improvement in quality of life (QOL), with large effect sizes for fatigue. Other authors tried to demonstrate effectiveness of exercise training at home but the result are contradictory and do not allow to conclude [27,28]. In a recent publication, Hogan et al. [29] compared in a RCT, 4 groups of patients who performed group physiotherapy (balance and strengthening exercises), individual physiotherapy, yoga group or a control group. They performed 1 hour a week during 10 weeks. All interventions showed a statistically significant improvement on balance tested with BBS which was better than the control group. These data provide preliminary evidence that 10-week interventions consisting of balance and strengthening exercises improve balance in high disabled MS patients [29].

**Physical agents**

**Electrotherapy**

Transcutaneous electrical nerve stimulation (TENS) did not improve with significant level, balance and mobility in MS [10]. Only few studies showed that TENS may decrease neurological pain and spasticity [10,30,31]. Functional electrical stimulation (FES) for foot drop was introduced by Liberson et al. in the 1960s [32]. This technique uses surface electrodes to trigger the deep peroneal nerve to activate the anterior tibialis to produce ankle dorsiflexion. Recent investigations have shown substantial benefit for the PwMS [33]. But it seems that some criteria have to be taken into account before proposing FES: ability to achieve neutral dorsiflexion, skin tolerance, cognitive capacity or support system to manage technology. Patients should also be emotionally stable with realistic expectations, and respect contraindications.

Neuromodulation that directly stimulates the peripheral or CNS to improve motor impairments is still being investigated although non-demonstrated actually [34-36]. Cranial nerve non-invasive neuromodulation was recently used by Tyler et al. [36] to improve gait in 20 chronic patients with moderate disability due to MS. The authors propose to use the tongue like interface to send electrical signals to the CNS, a technique already used in other studies to treat balance impairment [37-41]. Twenty MS patients with gait abnormality (EDSS: 3.5 to 6.0) participated in this double blind RCT study and were allocated to 2 groups experimental/control. Experimental group used a device that provide electrical stimulation of the tongue by a portable neuromodulation stimulator worn into the mouth and rest on the anterior, superior part of the tongue. Control group used a device that provides a stimulus that was not perceivable. Both group completed a 14-week intervention program including combination of exercise (balance exercises, gait training and relaxation) and the tongue stimulator. Results have shown greater improvement in gait assessed by the dynamic gait index (DGI) in the experimental group than control (P < 0.001) [36]. This pilot RCT complements a growing body of evidence demonstrating that combining electrical stimulation with exercise training may contribute to have positive effect on motor control for people with MS.

Actually these different techniques TENS, repetitive magnetic stimulation, electromagnetic therapy, have not been enough scientifically studied in RCT and were not able to prove their superiority to any other techniques used in rehabilitation therapy.

**Cooling therapy**

It is estimated that 60–80% of the MS population experiences transient and temporary worsening of clinical signs and neurological symptoms as a result of elevated body temperature [42–44]. Conversely, decreasing body temperature increases the conduction and may cause alleviation of the symptoms [45–47]. It is thought that the improvement observed clinically due to cooling is related to the temperature change in structures adjacent to demyelinated axons [48,49]. Some metabolic changes may have an effect on axonal transmission, and white blood cells nitric oxide (NO) levels and other inflammatory mediators such as cytokines may be affected from cooling process. The conduction in demyelinated axons is particularly sensitive to block by NO. The inflammation may directly cause symptoms via NO release, and its inhibition may lead to the improvement of symptoms [50]. Different devices were evaluated to provide cooling effect in body for PwMS like cold pack, cold bath, cooling suit and iced ingested blank [10]. Gait impairment improvement and the therapeutic effects of cooling in PwMS have not been convincingly demonstrated because studies were limited by uncontrolled designs, unblinded evaluations, reliance on subjective outcome measures, and small sample sizes [51]. However, in clinical practice cooling therapy could be considered as a potential adjunct to other symptomatic therapy in MS.

**Hydrotherapy**

Hydrotherapy is frequently applied to patient with painful neurological or musculoskeletal alterations [52]. In MS, many programs of exercises have used aquatic training. Castro-Sánchez et al., in 2012 [53], investigated the effectiveness of an Ai-Chi aquatic program proposed to 73 moderately disabled MS patients randomly assigned to an experimental or control group, who performed twice weekly, 20 weeks treatment program.
The experimental group decreased significantly pain levels and improved fatigue, spasms, depression and QOL, with no adverse effects. These beneficial effects lasted for 4 and 10 weeks after the end of the program and were superior to those obtained in the control group [53]. The lack of studies analysing the effectiveness on balance and gait performance of hydrotherapy or balneotherapy alone does not enable us to draw any conclusion, but this technique may be useful and moreover does not provide any serious adverse event in this population.

**Whole body vibration**

A Cochrane review published in 2012 [54] examines the efficacy of whole body vibration (WBV) in neurodegenerative disease. Only 4 studies for MS were included and the quality of the studies was methodologically low and inconsistent [55-58]. Regarding balance, mobility and muscle performance, the analysis did not show any statistically significant difference between groups. The evidence about its efficacy is weak and no strong conclusions can be derived [54].

**Orthotics devices and robot-assisted gait rehabilitation**

MS patients are frequently prescribed ankle-foot orthoses (AFO) to improve gait performance and to counteract muscular strength deficit and balance impairment. Literature on effectiveness of AFOs on walking ability of PwMS is very limited and it is difficult to draw any conclusions. However, published data suggest that the benefit of AFO is greater for more disabled patients [33]. Textured insoles are currently proposed in practice to increase plantar stimulation and modified balance [59-62]. A small study on 14 MS reported some effects on gait [63]. Dixon et al. investigated the immediate and delay effect of textured insoles on balance and gait in 46 PwMS (EDSS 0-6) [64]. Patients were allocated at random to wear one type of textured insoles (type 1, 2 and control) for 2 weeks. This study found that textured insoles had no immediate effects on balance or gait. After 2 weeks of wear, only some aspects of gait were improved but no balance parameters. More scientific studies exploring the effect of wearing insole in MS are needed to conclude.

Since the late 1990s, robot-assisted gait rehabilitation has become popular in neurological rehabilitation. Different systems are commercially available on the market, including the Lokomat® and the Gait trainer® [65]. Actually, TT, with or without body weight support (BWS) and/or robot-assisted gait training (RAGT), is a frequently used technique for gait rehabilitation in neurological diseases [65]. Only a few studies have been published that investigated gait-related outcome measurements, after robot-assisted gait rehabilitation in PwMS. The results show that TT, with BWS or RAGT improve walking speed and walk perimeter in persons with MS, but it is difficult to define what kind of TT intervention is the most effective [65]. Therefore, RCTs with larger but more homogeneous populations are needed. Recently, one single blind RCT included 22 PwMS (EDSS 1.5-6.5) compared the effectiveness of RAGT and sensory integration balance training in improving walking and balance performance [66]. Results shown that RAGT and balance exercise might improve step length, postural stability and the level of balance perceived during performs ADL. These results may be maintained for 1 month after the end of the program [66]. In the precedent studies, authors did not find difference between RAGT efficacy and walking training on gait performance [67-71]. Almost, the conventional walking exercise appeared to have better long-term positive result on postural control compared to RAGT [66]. However, from a clinical perspective it seem that RAGT could be another rehabilitation strategy for high disabled patients with MS.

**Multidisciplinary rehabilitation**

Common multidisciplinary rehabilitation team members include physician, physical therapist, occupational therapist, speech pathologist and social worker. Multidisciplinary rehabilitation programs include outpatient rehabilitation, inpatient rehabilitation program and home-based programs. Multidisciplinary rehabilitation has shown short positive effects on activity and participation in PwMS [11,72]. Inpatient and outpatient program have demonstrated improvement in functional status [72,73], motor function [74], QOL, disability, balance and mobility [75,76]. Inpatient multidisciplinary rehabilitation programs of high intensity may have shorter effects, whereas outpatient of lower intensity but longer duration may result in longer term improvement in QOL [72]. However, multidisciplinary positive effects were reported in a small sample, with poor methodological quality. These results highlighted the need for high quality RCT to assess the effectiveness of specific rehabilitation intervention, the appropriate intensity and objective of therapy, the cost-effectiveness of multidisciplinary rehabilitation program [77,78].

**Home-based program and telerehabilitation**

The outcome of exercises performed in a hospital setting or at home in terms of effectiveness, cost and psychological effects are controversial. Although the rehabilitation programs held in a hospital setting seem to have a greater effect, various studies carried out at home are also effective [79-81]. Home-based rehabilitation was proposed since the 1990s for MS patient to promote physical activity or improve functional capacities and QOL [76,82-84]. More recently Carter et al. [85] have shown that a mixed (supervised and home-based) pragmatic exercise intervention for self-directed exercise in people with mild to moderate disability due to MS is feasible, with excellent retention and high compliance rates. Results also suggest important behavioural and QOL benefits that are retained for at least 3 months [85]. Aydin et al., in 2014 [86], compared
effectiveness of home-based or hospital-based callisthenic exercises in PwMS (EDSS < 4.5). Both group were applied exercises program 5 days per week (1-hourly session) of callisthenic exercises 3 days and relaxation 2 days during 12 weeks. After 12-week exercise program, the home-based and hospital-based exercise groups showed significant improvements in terms of balance, gait, psychological status and QOL but no difference on fatigue measurement. Callisthenic exercises are simple and economical as they do not require any devices and can be performed either at home or in a hospital setting.

Home-based rehabilitation seems to be useful for patient with MS to enhance activity and QOL but patients need to be trained on how to perform the exercises by physical therapist specialized in the treatment of PwMS. The follow-up and the supervision of the exercises are very important to review exercises barriers and motivate the patient to participate in the exercise program.

Interest has recently increased with regard to the development of e-health projects. The cost-effectiveness and its financing are being actively discussed in various chronic diseases [87-89]. In the context of e-health, TR consists in delivery of rehabilitation services via electronic systems using information and communication technologies [90]. Recently, studies relating the use of virtual reality (VR) and video games consoles have proliferated in the field of neuro-rehabilitation. Interactive multimedia technologies offer some advantages over traditional rehabilitation treatment either due to accessibility issues, geography or treatment availability, providing motivational activities, therapeutic adherence and treatment compliance [91].

Finkelstein et al. first published a pilot study on home-based TR program in MS patients and have shown that TR is feasible and can potentially improve patient functional status significantly. Furthermore, participants demonstrated a very high support to home-based TR program [92]. More recently, Paul et al. [93] in a RCT have compared twelve weeks of individualized web-based physiotherapy completed twice per week or usual care (control). Results have shown that a 12-week individualized web-based physiotherapy is feasible and acceptable to people moderately affected with MS (EDSS < 6) but there was no statistically significant difference in the primary outcome measure, the timed 25 foot-walk-test in the intervention group. Authors conclude that web-physiotherapy could be useful for people who have problems accessing traditional services, offers more flexibility and allows patients to access physiotherapy regardless of day, time and geographical location.

Studies using Wii fit balance exercises have shown promising results in improving static and dynamic balance in PwMS [94-97]. In a non-randomised pilot study, Plow et al. [94] found that PwMS who have mild to moderate balance and mobility impairments can use Wii fit safely at home [94]. However Wii use declined after 3 months. Authors suggested that a more person-centred approach and regular follow-up might help to promote longer term Wii use. Nilsagard et al. [95] in a multi-centre RCT including 84 PwMS found significant improvements in dynamic balance in Wii fit group (2/day for 6 weeks) but no significant differences were found when compared with control group [95]. Improvement in static and dynamic balance has also been reported after 4 weeks training in the Wii fit 3 times a week [96], and after 12 weeks of daily training [97].

Some qualitative studies have explored effectiveness, feasibility and how intervention can be incorporated in clinical practice. A study including PwMS reported that a Wii fit home exercise program helped participants build confidence in their capacities, but usability of the Wii fit was limited by physical impairments [98]. Forsberg et al. [99] evaluated experience of using Wii fit for balance exercise from the perspective of PwMS and their physiotherapists. The effects of Wii Fit training were considered a fun and challenging way to improve balance impairment in MS in both group (patients and physiotherapist). The competitive aspect of the games provides feedback which was appreciated by PwMS and therapist. Wii fit may be a feasible alternative training that can be performed at home or in a rehabilitation clinic [99].

Gutiérrez et al. [100] explored the effect of a VR training program to improve balance and postural control in PwMS (EDSS 3-5). The control group (n = 25) received physiotherapy treatment twice a week (40 min) and the experimental group (n = 25) received individual TR training using the Xbox360© console with Microsoft® Kinect (4 sessions per week). The treatment schedule lasted 10 weeks for both group. The results demonstrated improvements in the balance and postural control of PwMS either in a TR using VR Technology or a conventional rehabilitation program.

TR provides some promising results in PwMS even though additional research is needed to evaluate the ability of these technologies to treat other symptoms associated with MS. We do not have any answers yet about cost-effectiveness and QOL impact of these technologies in this population.

Conclusion

Three main physiotherapeutic approaches based on models of motor control seem to be interesting for PwMS: muscle rehabilitation (biofeedback, aerobic training and muscle strengthening), neurotherapeutic facilitation (Vojta reflex locomotion, Brunnström, Rood, Bobath, proprioceptive neuromuscular facilitation) and the task-oriented approach (Constraint-Induced Movement Therapy, Motor Relearning Programme, modified Bobath concept, locomotor training and Dual Tasking methods). TENS, repetitive magnetic stimulation, electromagnetic therapy, WBV and RAGT are insufficiently studied in scientifically RCT and did not prove their superiority to other techniques used in rehabilitation therapy. Effectiveness of cooling therapy, hydrotherapy, orthoses and textured insoles has not been demonstrated by large RCT but they could represent a complementary
service to other PT technique in specific indications. Inpatient or outpatient multidisciplinary rehabilitation program need to be evaluated more precisely by large high quality RCT, but positive effects were reported with high satisfaction for PwMS. Home-based rehabilitation program have been developed and have shown promising results. New technology like TR using serious game and VR seem to be an interesting technique to promote physical activity and enhance QOL. TR is a resource to promote self-management and may reduce costs and future demand on health services. However, further research is required in PwMS.

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References
