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SYSTEMATIC REVIEW

THE ITALIAN CONSENSUS CONFERENCE CICERONE

What does evidence tell us about the use of gait robotic devices in patients with multiple sclerosis?

A comprehensive systematic review on functional outcomes and clinical recommendations

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ABSTRACT

INTRODUCTION: There is growing evidence on the efficacy of gait robotic rehabilitation in patients with multiple sclerosis (MS), but most of the studies have focused on gait parameters. Moreover, clear indications on the clinical use of robotics still lack. As part of the CICERONE Italian Consensus on Robotic Rehabilitation, the aim of this systematic review was to investigate the existing evidence concerning the role of lower limb robotic rehabilitation in improving functional recovery in patients with MS.

EVIDENCE ACQUISITION: We searched for and systematically reviewed evidence-based studies on gait robotic rehabilitation in MS, between January 1st, 2010 and December 31st, 2020, in the following databases: Cochrane Library, PEDro, PubMed and Google Scholar. The study quality was assessed by the 16-item assessment of multiple systematic reviews 2 (AMSTAR 2) and the 10-item PEDro scale for the other research studies.

EVIDENCE SYNTHESIS: After an accurate screening, only 17 papers were included in the review, and most of them (13 RCT) had a level II evidence. Most of the studies used the Lokomat as a grounded robotic device, two investigated the efficacy of end-effectors and two powered exoskeletons. Generally speaking, robotic treatment has beneficial effects on gait speed, endurance and balance with comparable outcomes to those of conventional treatments. However, in more severe patients (EDSS >6), robotics leads to better functional outcomes. Notably, after gait training with robotics (especially when coupled to virtual reality) MS patients also reach better non-motor outcomes, including spasticity, fatigue, pain, psychological well-being and quality of life. Unfortunately, no clinical indications emerge on the treatment protocols.

CONCLUSIONS: The present comprehensive systematic review highlights the potential beneficial role on functional outcomes of the lower limb robotic devices in people with MS. Future studies are warranted to evaluate the role of robotics not only for walking and balance outcomes, but also for other gait-training-related benefits, to identify appropriate outcome measures related to a specific subgroup of MS subjects' disease severity.

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KEY WORDS: Gait; Rehabilitation; Robotics; Lower extremity; Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), which causes demyelination and neurodegeneration. MS is often correlated with progressive disability and, in a high percentage of patients (75-85%) gait impairment is the main concern.[1] Even though walking difficulties are more prevalent in the chronic phase of the disease, subtle changes of gait parameters may be detectable even in the early phase.[1]

The Expanded Disability Status Scale (EDSS), first proposed by Kurtzke in 1983, classifies the degree of disability in MS patients.[2] This scale quantifies disability in 8 different systems, including pyramidal, cerebellar, visual, perceptual, cognitive, visceral, cerebral and brainstem level, and further classifies patients based on their residual deambulatory ability. Indeed, a score up to 3.5 defines a mild to moderate impairment of functional autonomy, whilst scores >7.5 identifies severe disability, up to patients bound on the wheelchair or bedridden. It is recognized that the distance walked by a patient with MS gradually diminishes as the illness progresses. Specifically, the gait of MS patients shows reduced speed, stride length and resistance as well as an increase in time spent in the double support phase.[1, 2]

Physiotherapy treatments focusing on gait training have generally proven beneficial and effective in improving gait and mobility as well as reducing the risk of a fall. In patients with more severe gait disabilities, however, overground walking training becomes difficult or even impossible.[3] More recently, the medical community has employed new approaches to gait training, which are based either on neuroplasticity, high-intensity training with a high number of task-oriented repetitions, or on robotics.[4] Initially, a body-weight-supported treadmill (BWST) was used for these newer types of training treatments. Later, motorized robotic systems associated with treadmill and BWST were developed. This type of approach, which reduces the strain on physiotherapists, is referred to as robotic-assisted gait training (RAGT).[5]

Furthermore, robotic exoskeletons have been developed in the past few years, to assist with lower limb gait movements and train overground (EAGT). These powered exoskeletons are used for either neurorehabilitation or as assistive devices.[6] Robotic training can increase the length, intensity, and the number of physiotherapy sessions, improving functional outcomes in neurological patients and reducing therapist burden and potentially healthcare costs.[7, 8]

Rationale and aim

There is growing evidence on the efficacy of RAGT in MS patients, but most of the studies have focused on gait parameters.[9] Indeed, most studies on this patient population showed significant effects of stationary RAGT for walking speed and endurance, balance as well as quality of life[4, 5, 9] Some works suggested superior clinical effects of RAGT with conventional treatment in more severe MS, but evidence is inconsistent.[4] Moreover, clear indications on the clinical use of robotics in the rehabilitation of lower limb still lack.

The aim of this review was to investigate the existing evidence concerning the role of robotic rehabilitation in improving lower limb functional recovery in patients with MS. In detail, following the CICERONE consensus suggestions, we aimed at evaluating:

- 1) the scientific evidence regarding the effects of robot-assisted rehabilitation on walking disorders and on the recovery of the lower limb in adults with MS, defining:
  - a) which types of devices are used and in which categories of patients;
  - b) what are the treatment protocols (duration, number of sessions, frequency, etc.);
  - c) what are the possible therapeutic approaches combined to the robot- assisted treatment and the comparison treatments;
  - d) what are the treatment outcomes / objectives, besides gait and balance;
- 2) the level of evidence regarding the effects of robot-assisted rehabilitation on walking disorders and on the recovery of the lower limb in adults with MS.

We also sought to give some evidence-based recommendations for the use of the main lower limb devices in the clinical settings.

Evidence acquisition

Search strategy

Several searches were performed on the following databases: Cochrane Library, PEDro, PubMed and Google Scholar, using the following key words: “robotic rehabilitation” and/or “end effector”; “exoskeleton” and/or “neurorehabilitation” and/or “functional outcomes” or “RAGT” or “Lokomat,” and/or “pain” and/or “spasticity” combined with the expression “multiple sclerosis.”

Inclusion/exclusion criteria and paper analysis

We included all of the systematic reviews, randomized clinical trials (RCT) and pilot studies published between January 1st, 2010 and December 31st, 2020 referring to MS rehabilitation using robotics. To be included, papers should deal with robotic devices (with or without VR or BWS), being a robot defined as “a re-programmable, multi-functional manipulator designed to move material, parts, or specialized devices through variable programmed motions to accomplish a task thanks to a peripheral feedback.” Indeed, studies with other kinds of electromedical devices were excluded. Different functional outcomes, including spasticity and pain, were considered.

Titles and abstracts were screened and full-text papers reviewed independently by two reviewers (R.S.C. and A.C.) using predetermined criteria. In case of disagreement, an independent reviewer fixed the problem (D.B.). Reviewers identified information, treatment recommendations and their level of evidence/grade of recommendations (when available). Moreover, each paper was checked for the year, edition, country, national/international and information contained. As this was intended only as a comprehensive review, we did not perform a metanalysis of the data.

Study quality assessment

The study quality was assessed by the 16-item Assessment of multiple systematic reviews 2 (AMSTAR 2) and the 10-item PEDro scale for the other research studies. Four different authors rated the studies included in this systematic review. Moreover, based on the Oxford Center for Evidence-Based (OCEBM) 2011 Levels of Evidence, systematic reviews were given level I, RCT level II, and parallel group, controlled trials level III. Case series, which have a level IV, were not considered.[10]

Evidence synthesis

After a first screening of 286 articles, a total of 35 published papers were selected, and from these 17 met the inclusion criteria and were analyzed (Figure 1). It was found

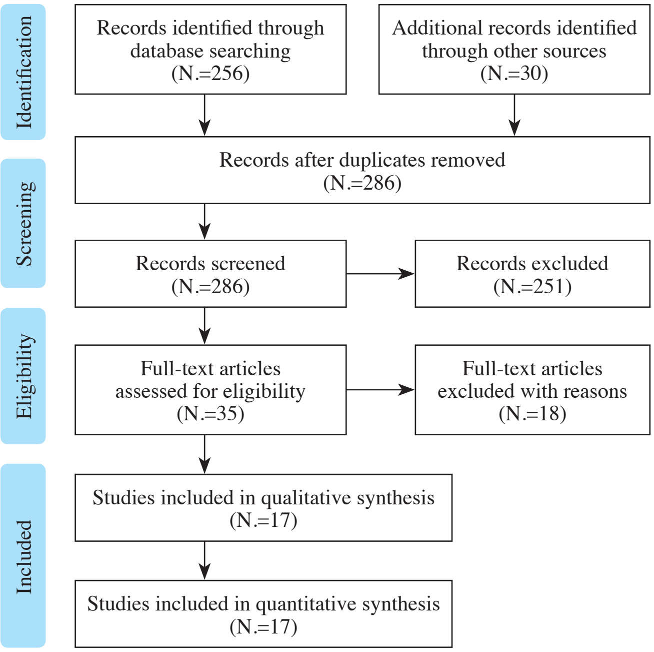

Figure 1.—PRISMA flow diagram for study selection.

that the 12 excluded articles were not relevant, as they investigated only treadmill treatments, telerehabilitation, or virtual reality treatments. Among the 17 selected articles, two are reviews of the literature,[11, 12] 13 are RCT,[13-26] and one[27] single group-pilot study. Two of the included RCT, were only accessible as abstracts,[22, 26] but with sufficient data to be considered in this review. Concerning the evidence level, level I was assigned only to the two reviews, level II to the 13 RCT, and level III to the single group-pilot study.

The sample size of the selected RCT ranges from 10 to 72 patients, with a median of 32. The two reviews respectively include 309 patients from nine studies, and 205 patients from seven studies.[11, 12] The studies investigated various kinds of robotic devices. Firstly, 13 of them[11-14, 17-19, 21-26] investigated RAGT (and all of them with the Lokomat device), where robotic assistance is applied to the hip and the knee, in conjunction with a treadmill. Two studies[15, 16] investigated RAGT using an end-effector (*i.e.* a device controlling the distal part of the lower limb with a mobile platform). One study[20] evaluated the Keeogo, an overground exoskeleton attached to the pelvis and to both lower limbs, assisting the hip and the knee robotically, and allowing the patients to wear their habitual leg-foot orthosis. Lastly, a study[27] investigated the EKSO-GT exoskeleton.

The patients included in the studies presented with moderate to severe ambulation disability. In only two studies the minimal EDSS score was 1.5 to 3.5, identifying a low disability ambulation level. In the other studies the minimal EDSS score was 4 to 6. Generally speaking, the patients included in the review had almost at least minimal residual ambulation capacity, given that the higher EDSS score was 7.5.

Nine RCT[13, 16-19, 23-26] and both literature reviews[11, 12] compared the efficacy of RAGT treatments with the conventional overground gait training (CGT). An RCT[21] compared RAGT with either gait training on a treadmill (TT), or gait training using a TT with BWST (TT-BWST). Two RCT[14, 22] compared RAGT treatment with the use of RAGT and virtual reality (VR) in conjunction. Lastly, one RCT study[15] compared RAGT with the Sensory Integration Balance Training (SIBT). The efficacy of overground exoskeletons was either compared with CGT,[20] or investigated separately by using a single-group pilot study.[27] The VR and SIBT were combined with the robot assisted treatment, whereas CGT and TT or TT-BWST were really comparison treatments, as they did not use robotics.

In the studies dealing with RAGT (using either the Lokomat or the Reha Stim), the effective duration of treatment was 30-40 mins per session. The number of sessions per week ranged from 2 to 5, depending on the study. The total length of treatment ranged between 3-8 weeks, with a maximum length of 18 weeks, reported only by one study. The length and duration of EAGT and RAGT treatments were comparable. The duration of the robotic training was longer in the case of the exoskeleton Keeogo, since it can be executed at home. In fact, the patient can wear the device for the entire day and remove it during daily activities and during sleep. In some studies, a robotic treatment was administered in conjunction with conventional treatment.[13, 14, 16, 17, 25] In all of these studies, the type of conventional training was based on muscle exercises

TABLE I.—*Outcome measures assessed in each of the articles selected for this work.*[11-27]

Outcome measure	Research articles																
Reference number	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Gait speed	X		X		X	X	X		X	X	X	X		X			X
Gait resistance	X		X	X		X	X	X	X	X	X	X	X	X		X	X
Motor skills		X		X	X	X	X	X			X		X	X	X	X	X
Balance		X			X	X	X					X		X	X	X	X
Functional autonomy		X		X		X									X		
Spasticity		X		X	X		X										
Fatigue				X			X							X			
Disability				X		X				X					X		
Quality of life					X	X	X					X		X			
Depression		X													X		
Kinematic parameters	X									X			X			X	X
Muscular strength	X	X															
Energy expenditure											X						
Activity level					X												
Pain					X												
Cognitive abilities		X										X					

X: the study has assessed that specific outcome variable.

without overground gait training, and associated with additional approaches, such as hippotherapy,[13] occupational therapy,[13, 16, 17] hydrotherapy,[13, 17] or cognitive neuropsychological treatments.[13, 16]

Several outcome measures were evaluated in the studies selected (Table I) (Supplementary Digital Material 1: Supplementary Table I, Supplementary Table II),[11-27] being gait speed and endurance the most used. RAGT, with regard to the Lokomat, has proven feasible and significantly effective, especially in MS patients presenting with severe disability (EDSS 6-7.5), and have shown the potential in improving gait speed and endurance,[11, 13, 19, 25] as well as increasing muscular strength.[13] In patients with a similar degree of disability, training with the end effector Reha Stim was also effective, and resulted in increased gait endurance, reduced spasticity and effort with a consequent improvement in autonomy in ADLs.[16]

Exoskeleton treatment with Keoogo was tested on patients with moderate gait impairment (EDSS <6.5), and it showed to be effective in improving gait resistance and in reducing the time needed to climb up the stairs. On the other hand, it had no impact on the total physical effort, measured in the number of steps/daily, or on the dynamic motor skills.[20] Over-ground exoskeleton treatment, tested on patients with EDSS of 6-7.5, was instead significantly effective in improving walking speed on short distances and in reducing energy expenditure.[27]

Conventional over-ground walking high-intensity training was particularly effective in improving most of the temporal parameters of walking.[11, 17, 19] Therefore, the conclusions from these latter RCT studies and from one of the two reviews[11] were that RAGT treatment has beneficial effects on gait parameters and endurance which are comparable to those of conventional treatments.[11, 18, 19] The improvements in gait speed and endurance were slightly more pronounced following RAGT treatments, but the comparison with conventional treatments did not yield significant differences. The other included review instead concluded that robotic training is always more effective in improving gait endurance compared to more conventional treatments, but the results are not considered sufficient to make significant clinical conclusions.[12] In general, the data tends to show that RAGT treatments seem more beneficial in patients with a more severe degree of disability (EDSS 6-7.5),[11, 13, 16] while traditional treatments seem more beneficial in patients with a less severe degree of disability as well as a higher walking speed.[17]

When comparing BWSTT and RAGT in conjunction with treadmill gait training (BWSTT-RAGT), both treatments were equally effective in improving outcome measures. No superiority of robotic treatment with RAGT was found over BWSTT alone (20). RAGT treatments with Lokomat/Reha Stim in conjunction with VR show to have an additional benefit, as they improve cognitive outcomes as well.[14, 22, 25]

Lastly, follow-up measurements showed that the benefits of the various treatments were still present one month and three months after the treatments. On the other hand, the studies with follow-up measurement after six months highlighted that the treatments have no long-term positive effects.[13, 15, 22, 26]

Discussion

This is the first time ever that a review has comprehensively investigated all of the main functional outcomes related to the lower limb after treatment with gait robotic devices. Indeed, most of the published systematic reviews have mainly focused on gait and balance,[9, 11, 12] overseeing other important aspects following robotic neurorehabilitation.

According to the existing data,[9, 12] our work demonstrates that training with robotic devices, such as Lokomat or Reha-Stim, is feasible and significantly effective in MS patients and has shown the potential to improve gait speed, gait endurance and balance. Recovery of walking continues to be the primary goal for individuals with neurological deficits, including MS, and a contributing factor to the quality of life. Therefore, relearning to walk is considered a major goal during neurorehabilitation. Although the optimal therapeutic intervention to achieve full recovery of gait remains unknown, any rehabilitation effort intended to drive changes toward motor recovery should incorporate principles of neuroplasticity. This is the reason why, in the last years, we have witnessed a growing development and use of robotics in the rehab field, as it is able to train the patients in an intensive, repetitive and task-oriented manner so as to boost neural plasticity.[5, 28]

In their systematic review, Bowman *et al.*[9] have found that RAGT improves balance and gait outcomes in a clinically meaningful way in the MS population. RAGT seemed more effective if compared to unspecific rehabilitation, while it showed similar effects when compared to specific balance and gait training in studies with level II evidence. The review by Yeah *et al*. showed comparable improvement in primary outcomes, including gait speed, gait endurance, stride length and balance as well ambulation between RAGT and conventional walking training in people with MS. Differently from our work, Yeah *et al.*

mainly focused on gait parameters and performed a metanalysis with pooled data involving 312 patients. A recent systematic review with meta-analyses and meta-regressions suggested that RAGT was not significantly more effective than CGT to train walking in people in MS.[11] However, this work included a low number of studies (as it did not use a comprehensive approach as we did in our work) with a low variability of disabilities at baseline.

Although it is not possible to reach firm conclusion on the effect, robotics has several advantages in terms of patient motor assistance, intensity of training, safety, and the possibility to combine other therapeutic approaches. Moreover, even if not all of the patients undergoing robotics might improve gait and balance, they may benefit from this type of training regarding non-motor outcomes, including spasticity.[29] Notably, better improvements in spasticity have been demonstrated when robotics is coupled with drugs acting as neuromodulators, including nabiximols.[30] This further demonstrates how combined approaches (*i.e.* robotics plus drugs, VR, conventional training, non-invasive neuromodulation, and other cues including music) are more able to potentiate neural plasticity maybe through a sort of a paired associative stimulation. Our comprehensive review found improvement in several types of non-motor outcomes, including pain, fatigue, depression, and quality of life. Yeah *et al.*[4] found that after the intervention individuals receiving RAGT felt less fatigue and spasticity than those undergoing conventional training. Nonetheless, this systematic review has evaluated neither cognitive and behavioral outcomes nor the relationship between the outcomes and the disability level, differently from our work.

The positive effects of robotics on non-motor outcomes agree with the data coming from patients affected by stroke.[31] Indeed, EAGT has been demonstrated to have better outcomes than conventional training in constipation, mood, and coping strategies (with regard to social support), as well as in the perception of quality of life. As constipation is a serious problem in MS patients with moderate-severe disability, it would be interesting to evaluate if this symptom would improve in such patients after robotic training. What is more, several studies are demonstrating the psychological and cognitive effects of post-robotic training, especially when the device is associated with VR.[32] VR can be used to provide the patient with repetitive, task-specific training that, thanks to the multisensory feedback, and can potentiate the use-dependent plasticity processes within the sensory-motor cortex, thus promoting/enhancing functional motor recovery. The tool enables the patient to perceive the environment as real, then increasing the patient's engagement and embodiment.[31] As regards the studies investigated in our review, the combination of robotics with VR was linked with additional benefits on cognitive functions and balance of patients with MS (Level of Evidence: II).

Notably, the benefits associated with these types of robotic treatments (especially when coupled to VR) are not strictly related to motor ambulation skills or energy expenditure, but also have positive effects on autonomy, spasticity, fatigue, well-being, cognition and quality of life in patients with MS. For this reason, it is always recommended to employ measurement scales, which assess these parameters, when administering a targeted treatment plan.[33] While for stroke there are some recommendations for the clinical use of robotic rehabilitation,[33] clear indications for MS are scarce. The studies we reviewed use heterogeneous scales or instrumental measurements: the gait speed (10MWS, T25FW, 20MWT, cm/s on treadmill, 3mWS); endurance (6mWT, 2mWT, 3mWT); motor ability (TUG/RMI/FAC); balance (BBS/ABC/SOT/SA/TBS); disability (FIM/mBI); spasticity (mAS/SEA); fatigue (FSS, WE bei MS); specific disability levels (EDSS); quality of life (MSQOL-54, SF36, VAS, EQ-5D, RAND-36, PHQ9); depression (HRSD); kinematic parameters of the path (step length, single support time, double support time); hip/knee muscle strength (instrumental with robot); energy expenditure (VO_2 peak); the level of activity (METs); pain (NRS); cognitive skills (COPE, PASAT, PFT, RBMT, DSymb). However, there are no recommendations for an essential core set that allows to have a homogeneous description of the RAGT functional outcomes in patients with MS. As Chee *et al.* found that at each point-increase in EDSS corresponds a reduction of speed and an increase of the risk of falling by 18%,[34] the tool could also be used to partially address this issue.

It is noteworthy that from the analysis of the recent literature on the topic there is no evidence of additional benefits from robotic devices when compared to gait conventional treatments, including over-ground walking (Level of Evidence: I) or treadmill training (with or without BWSTT) (Level of Evidence: II). However, this data refers to the whole MS population, without taking into consideration the disability level. When the patients' walking abilities are less impaired, overground gait training is preferred, especially if using high-intensity treatments. Indeed, treatment with robotic devices is advantageous when administered to the patients with a greater degree of disability and worse gait impairments (*i.e.* EDSS 6-7.5). This is in line with the work by Morone *et al.*, indicating how patients

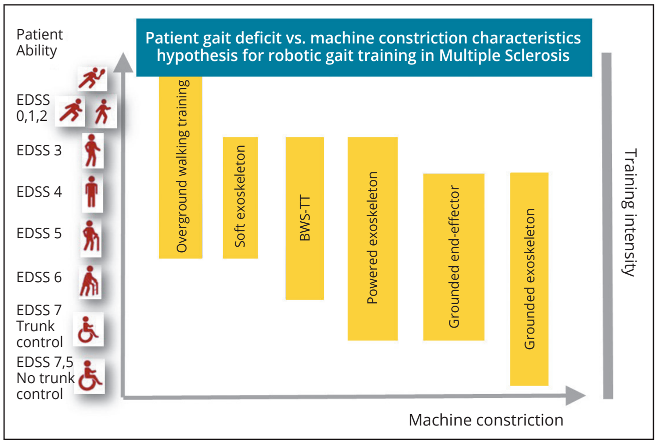

Figure 2.—Theoretical schema combining the patient's level of ability defined by EDSS with the best possible solution in terms of walking training and machine constriction.

with stroke may benefit from robotics depending on their disability level.[35] Based on the available literature data, to provide clinicians with practical indications about the use of robotics in clinical settings, we believe that different training with different approaches and kinds of devices should be used in the different stages of the disease, as per patients' EDSS. Indeed, according to principles of neurosciences, walking training should be done in the most physiological possible way. The more the severity of the subject affected by MS, the more the assistance and the constraint level provided by the robot/device, as shown in Figure 2. We have to specify that EDSS was the proposed method of quantifying disability of MS and monitoring changes in the level of disability over time, as it is widely used in clinical trials and also in clinical settings. Indeed, other useful scales, such as the 6MWT, can be used to assess a single outcome measure, whereas EDSS investigate different systems (including bowel and bladder problems) and it may provide a better relationship between RAGT and global functional outcome (as per aim of this review).

On the other hand, it has been demonstrated that RAGT was not superior to CT in improving gait speed in patients with progressive MS and severe gait disabilities where a positive, even transitory, effect of rehabilitation was observed.[36] This is why studies with more homogeneous samples (i.e. with the same type of SM and comparable disability level) are needed.

As the studies we reviewed used different treatment protocols, it is not possible to recommend a specific treatment duration, number of sessions and frequency. For many years, exercise was controversial in patients with MS and thought to exacerbate symptoms and fatigue. However, as it has been found that exercise is safe and effective, this has become a cornerstone of MS rehabilitation and may have even more fundamental benefits in MS.[37] Nonetheless, fatigue related to RAGT has been poorly investigated and preliminary data are encouraging, demonstrating how this symptom improves after robotic treatment.[14-17-24] For a better application of RAGT in clinical practice, specific protocols targeting this important issue and with higher involvement of the patients are necessary. Indeed, it has been shown that neurorehabilitation using innovative technologies can be useful for the commitment and motivation during the rehabilitation process, with possible positive effects on the functional and psychological outcomes of patients with MS.[38]

Importantly, while patients included in randomized controlled interventional trials have to fulfill many inclusion and exclusion criteria, data coming from real clinical settings are welcomed. To this end, the ARTIC network (an international group of diverse, clinically renowned centers whose goal is to advance the science of rehabilitation robotics) is evaluating the use of robotics (with regard to the Lokomat) in the real neurorehabilitation environment.[39] This network offers a unique opportunity to investigate the implementation, application, and effectiveness of rehabilitation technologies, proposing a valuable cue for clinical recommendations. Indeed, variation in practice among ARTIC members together with collection of common data and outcome measurements will enable the group to draw strong, generalizable conclusions. Further goals include establishing standardized treatment protocols and increasing medical and governmental acceptance of robotic therapy.

Finally, concerning long term outcomes, there is no comparison from treatment protocols although the beneficial effects of a high-intensity training tend to disappear at the follow-up period. About that, it is recommended to train patients regularly, *i.e.* every three or six months to maintain the gained robotic after-effects.

Limitations of the study

The systematic review had some limitations: the lack of risk of bias analysis, the wide variability in terms of robotic devices, of the training protocols, and of the outcome measures assessed. The studies included in this comprehensive review have several limitations too, including the small sample sizes, the lack of a control group and the lack of long-term follow up evaluations. Moreover, a metanalysis of the included studies was not performed and this prevent us from making interpretations on the magnitude of improvements found in RAGT literature, and whether this is approaching thresholds of clinical meaningful change. This latter change, however, has been demonstrated by other authors concerning gait and balance using a metanalysis of pooled data.[9] We have instead comprehensively considered all the outcomes following robotic gait training, showing how patients may benefit from robotic devices independently from their gait and balance recovery. A systematic review with metanalysis of non-motor-outcomes following RAGT should be performed in the near future.

Conclusions

The present comprehensive systematic review highlights the potential beneficial role of lower limb robotic devices on functional outcomes in subjects affected by MS. In particular, the robotic training showed similar beneficial effects of a matched dose of the standard therapy, with greater benefits in patients with a more severe disability. Clinical heterogeneity of treatment programs and the variety of robot devices could severely affect the generalizability of the study results. Future studies are warranted to evaluate the role of RAGT not only for walking and balance outcomes, but also for other gait-training-related benefits, to identify appropriate outcome measures related to a specific subgroup of MS subjects' severity.

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