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Telerehabilitation for persons with multiple sclerosis. A Cochrane review

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A wide range of telerehabilitation interventions are trialled in persons with multiple sclerosis (pwMS). However, the evidence for their effectiveness is unclear. Aim of the review was to systematically assess the effectiveness and safety of telerehabilitation intervention in pwMS, the types of approaches that are effective (setting, type, intensity) and the outcomes (impairment, activity limitation and participation) that are affected. The search strategy comprised: Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Review Group Specialised Register (up to 9 July, 2014). Relevant journals and reference lists of identified studies were screened for additional data. Selected studies included randomized and controlled clinical trials that compared telerehabilitation intervention/s in pwMS with a control intervention (such as lower level or different types of intervention, minimal intervention; waiting-list controls, no treatment or usual care; interventions given in different settings). Best evidence synthesis was based on methodological quality using the GRADEpro software. Nine RCTs (N.=531 participants, 469 included in analyses) investigated a variety of telerehabilitation interventions in adults with MS. The interventions evaluated were complex, with more than one rehabilitation component and included physical activity, educational, behavioural and symptom management programmes. All studies scored "low" on the methodological quality assessment. Evidence from included studies provides 'low-level' evidence for reduction in short-term disability (and symptoms) such as fatigue. There was also "low-level" evidence supporting telerehabilitation in the longer term for improved functional activities, impairments (such as fatigue, pain, insomnia); and participation. There were limited data on process evaluation (participants'/therapists' satisfaction) and no data available for cost effectiveness. There were no adverse events reported as a result of telerehabilitation intervention. There is limited evidence to date, on the efficacy of telerehabilitation in improving functional activities, fatigue and quality of life in adults with MS. There is also insufficient evidence to support what types of telerehabilitation interventions are effective, and in which setting. More robust trials are needed to build evidence for the clinical and cost effectiveness of these interventions.

Key words: Multiple sclerosis - Rehabilitation - Disability - Physician impairment.

Multiple sclerosis (MS) is a chronic neurological disease affecting approximately 1.3 million people worldwide.[1] The median estimated incidence of MS globally is 2.5 per 100,000 (with

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a range of 1.1 to 4), the prevalence about 30 per 100,000 population (range 5 to 80), and a female preponderance (female to male ratio of 3:1).[1, 2] The patterns of presentation in MS are heterogeneous and include: “relapsing remitting” (RR) MS (85%), characterised by exacerbations and remissions; “secondary progressive” (SP) MS with progressive disability acquired between attacks (in 70% to 75% who start with RRMS, it is estimated more than 50% will develop SPMS within 10 years, and 90% within 25 years); “primary progressive” (PP) MS (10%), where persons develop progressive disability from the onset; and “progressive relapsing” (PR) MS (5%), where persons begin worsening gradually and subsequently start to experience discrete attacks.[3, 4] The prognosis in MS is variable and difficult to predict, and depends on the type, severity and location of demyelinating lesions within the CNS.[4, 5] Various factors such as older age at onset, progressive disease course, multiple onset symptoms, pyramidal or cerebellar symptoms and a short interval between onset and first relapse are associated with worse prognosis.[5]

Persons with MS (pwMS) have a prolonged median survival time from the time of diagnosis of approximately 40 years.[3] Therefore, issues related to progressive disability (physical and cognitive), psychosocial adjustment and social re-integration progress over time. These have implications for pwMS, their carers, treating clinicians and society as a whole, in terms of healthcare access, provision of services and financial burden.[2, 6]

The pwMS can present with various combinations of deficits such as physical (motor weakness, spasticity, sensory dysfunction, visual loss, ataxia), fatigue, pain (neurogenic, musculoskeletal and mixed patterns), incontinence (urinary urgency, frequency), cognitive (memory, attention), psychosocial, behavioural and environmental problems, which limit a person’s activity (function) and participation.[7] Cognitive and behavioural problems can be subtle and often precede physical disability requiring long-term care.[8] The care needs in this population are complex and longer-term multidisciplinary management is recommended, both in hospital and in community settings.[7-9] Despite recent advances in MS management, many pwMS are unable to access these developments due to limited mobility, fatigue and related issues, plus costs associated with travel.

With increasing financial constraints on healthcare systems, alternative methods of service delivery in the community and over a longer term are now a priority. The emerging advances in information and communication technology (ICT) may present as an alternative efficient and cost-effective method to deliver rehabilitation treatment in a setting convenient to the patient. Telerehabilitation is an emerging method of delivering rehabilitation that uses ICT to serve patients and clinicians by minimising the barriers of distance, time and cost. The driving force behind this has been the need for an alternative to face-to-face intervention, enabling service delivery in the natural environment – that is, in patients’ homes.[10] It extends rehabilitative care beyond the hospital process and facilitates multifaceted, often psychotherapeutic approaches to modern management of pwMS.[11] It provides equal access to individuals who are geographically remote and to those who are physically and economically disadvantaged.[10, 12] It can improve the quality of rehabilitation delivered [10, 12-16] and gives healthcare providers an opportunity to evaluate the intervention previously prescribed, monitor adverse events and identify areas in need of improvement, which may not always be possible within the constraints of face-to-face treatment protocols in the current health systems.[10, 15] Telerehabilitation was reported to be effective in neurological conditions such as stroke (Legg 2004).[17] A wide range of telerehabilitation interventions are trialed in pwMS.[11, 18, 19] However, there is as yet no systematic review of telerehabilitation interventions in pwMS to guide treating clinicians on evidence for its validity, reliability, effectiveness and efficiency in this population.

The aim of this review was to assess the effectiveness and safety of telerehabilitation intervention in pwMS, especially the types of approaches that are effective (settings, intensity) and the outcomes that are affected.

Materials and methods

The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group search strategy identified all randomized (RCT) and controlled clinical trials (CCT) that compared telerehabilitation with routinely available local services or lower levels of intervention; or trials comparing in-

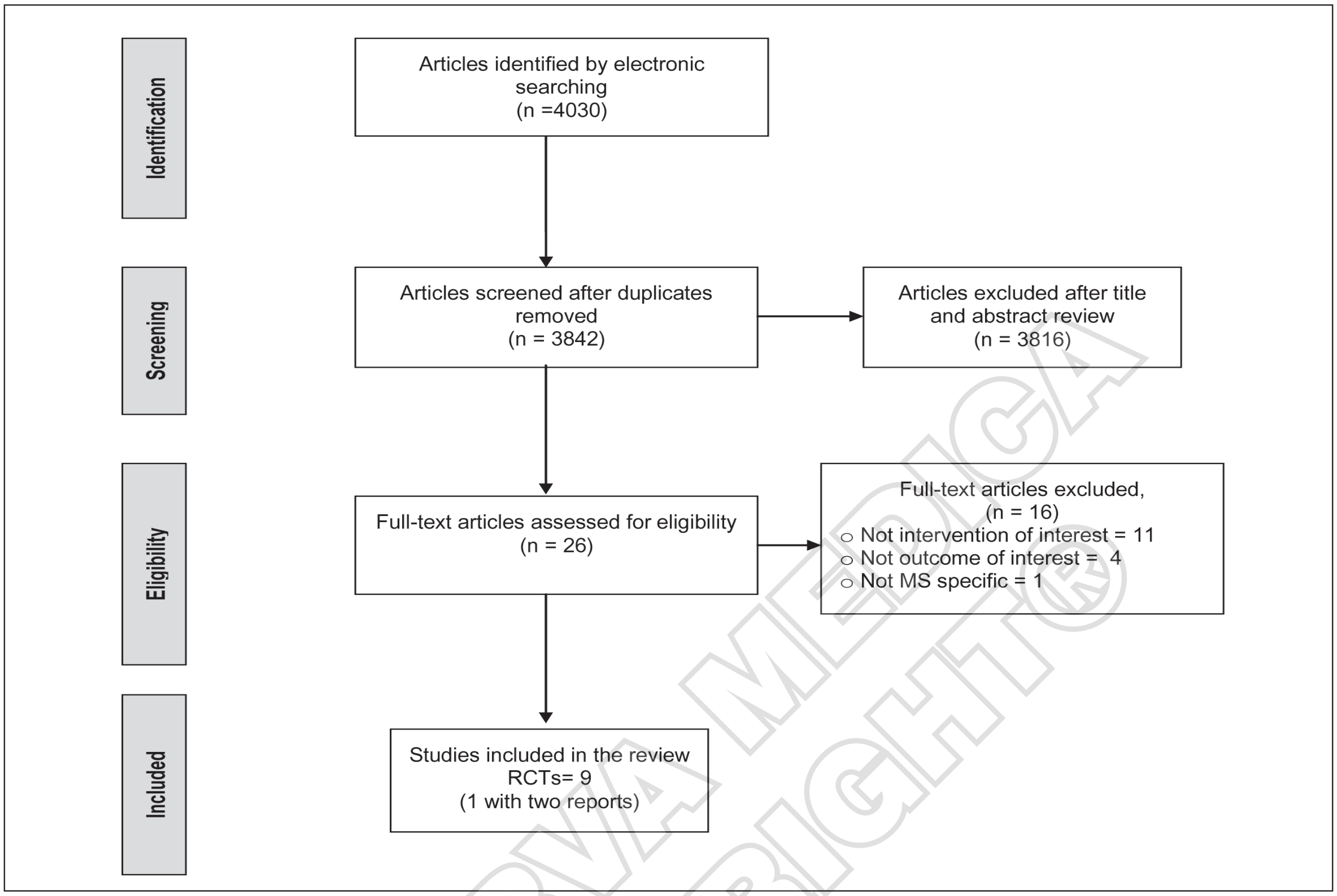

Figure 1.—Articles' selection process.

terventions in different settings or at different levels of intensity.

Three review authors selected trials and rated their methodological quality independently. Assessment of risk of bias was performed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADEpro) software according to the Cochrane Handbook of Systematic Reviews of Interventions,[19] from the domains: sequence generation, allocation concealment, blinding of participants, therapists and outcome assessors, incomplete outcome data and selective outcome reporting (details are available in the full review). Quantitative analysis was not possible due to limited number of studies identified and other clinical heterogeneity. Therefore qualitative synthesis of 'best evidence' was presented. Subgroup analysis was not possible due to lack of studies.

Results

Study characteristics

The literature search identified 4030 references (Medline=79; Embase=3799; Central=136; Cinahl=5; Lilacs=9; CRD database=0; Cochrane Opportunity Fund Project=0; Trial Registries *via* WHO Portal=0; handsearching journals=0; handsearching trial registries=2). Of these, the full text of 29 articles was retrieved for further assessment to determine inclusion in the review. In total, 9 RCTs,[11, 18, 21-27] one with two reports,[27, 28] published between 2003 and 2014 that compared various telerehabilitation interventions in pwMS with either routinely available local services or lower levels of intervention; or care in different settings or at different levels of intensity, fulfilled the inclusion criteria for this review (Figure 1). The included studies

TABLE I.—*Summary of included studies.*

Study Author, year, country	Objectives	Study type, participants number (N.)
Dlugonski (2012) [20] USA	To examine the effectiveness of internet delivered and theory-based behavioural intervention for increasing and sustaining physical activity	RCT, parallel group with wait-list controls N.=45: intervention group =22 and control =23 Assessment time points: Baseline, post-intervention, 3 months postintervention
Egner (2003) [17] USA	To examine longitudinal data on depression, fatigue and HRQOL in pwMS as part of a larger study of the impact of a telerehabilitation intervention (structured in home counselling) delivered via telephone or video on people with severe mobility impairment	RCT, three parallel groups N.=27: Group 1 (video) = 9; Group 2 (telephone) = 11 and Group 3 (standard care) = 7 Assessment time points: Baseline, week 5 during intervention, postintervention, and then on a monthly basis for 2 years
Finlayson (2011) [21] USA	To test the efficacy and effectiveness of a group-based, teleconference-delivered fatigue management program for pwMS	RCT, two group time series design with a wait-list control group N.=190: intervention group =94 and control group =96 Assessment time points: Baseline, 3 months, 6 months (postintervention)
Frevel and Maurer (2014) [22] Germany	To examine effectiveness of an Internet-based home training program (eTraining) in compared to hippotherapy to improve balance in pwMS	RCT, parallel group N.=18: intervention =9; control =9 Assessment time points: baseline, postintervention
Gutierrez (2013) [23] Spain	To demonstrate the potential improvements in postural control among pwMS who complete a telerehabilitation program	RCT, parallel group N.=50: treatment group =25 and control group =25 Assessment time points: baseline, postintervention
Huijen (2008) [11] Italy, Spain and Belgium	To investigate the feasibility of a telerehabilitation intervention for arm/hand function (the Home Care Activity Desk training) in a home setting in pwMS	RCT, parallel group, multi centred N.=81 (stroke=16, TBI=30, MS=35): intervention group=55 (MS=24) and control=26 (MS=11) Assessment time points: baseline, 1-month after usual care, and 1-month postintervention

Demographic characteristics	Summary of results	Author's conclusions
Mean age 46.6 years (SD: 9.7 years), 86.7% female, mean time since diagnosis 9.4 years (SD: 7.8 years), 64.4% had at least college degree, 95.6% Caucasian, 62.2% employed and 73.3% married	Physical activity (GLTEQ scores): Significant increase in physical activity in the intervention group compared to control group at post-intervention and 3-month follow-up assessments. There was no significant change in walking mobility, physical and psychological HRQOL at both post-intervention and 3-month follow up assessments in both groups; and no significant group difference between two groups for these variables.	The results support the efficacy of an internet-delivered behavioural intervention for increasing and sustaining physical activity in pwMS.
Mean age 46.0 years (SD: 9.0 years), 63% female, 44% married, 37% African-Americans and mean EDSS score of 7.8 (SD 0.6)	In overall, fatigue symptoms were far more prominent than depressive symptoms and affected 100% of the sample at month 12. Men exhibited significantly higher rates of depression than women. Participant in video group reported higher HRQOL scores and fatigue and lower depression scores for 24 months. Fatigue scores were significantly lower for the video group at month six, 12, and 18. At baseline, controlling for EDSS, depression and fatigue were correlated. However, no consistent relationship was observed over time between the two. Depression appears to peak at six months then decline, while fatigue remains relatively high over the two-year period.	Findings suggest that telerehabilitation interventions may be beneficial, although the results need confirmation through larger samples. In addition, the higher prevalence of male depression needs further investigation.
Mean age 42 years (SD approx.. 11), 9M 23F, mean disease duration 6 years (SD 7 years), mean Guy's Neurological Disability Scale=18 (SD=9)	The group-based, teleconference-delivered fatigue management program was more effective and efficacious for reducing fatigue impact but not fatigue severity. Before and after comparisons with the pooled sample demonstrated efficacy and effectiveness for fatigue impact, fatigue severity, and 6 of 8 HRQOL dimensions. Changes were maintained for 6 months with small to moderate effect sizes.	The results offer strong support for the viability of teleconference-delivered fatigue management education for enabling pwMS to manage fatigue.
Mean age 45.5 years (range 32-57), mean EDSS 3.8 (range 2-6), mean disease duration 19 (range 1-35), RRMS 67%	Both intervention groups showed comparable and highly significant improvement in static and dynamic balance capacity No difference was seen between the both intervention groups. Fatigue and quality of life improved only in hippotherapy group	An internet-based home training program, specialized on balance and postural control training, is feasible for balance and strength training in pwMS
Intervention group: mean age 39.7 years (SD 8.1), 54% women, mean disease duration 9.7 years (SD 6.8), EDSS score ≥4: 83.6%, RR MS: 71.9% Control group: mean age 42.8 years (SD 7.4), 61% women, mean disease duration 10.9 years (SD 5.4), EDSS score ≥4: 78.3%, RR MS: 65.2%	Improvement over general balance in both groups. Visual preference and the contribution of vestibular information yielded significant differences in the intervention group.	A telerehabilitation program based on a virtual reality system allows one to optimize the sensory information processing and integration systems necessary to maintain the balance and postural control of pwMS.
Intervention group: mean age: 47 years (SD 18) (MS 48 years (SD 12)), 71% male (MS 46% male), mean disease duration 9.7 years (SD 7.8 years) (MS 15.1 years (SD 8.6); Control group: mean age: 50 years (SD 18) (MS 51 years (SD 14)), 69% male (MS 64% male), mean disease duration 10.2 years (SD 7.6 years) (MS 15.6 years (SD 7.8)	Overall arm function (ARAT score) slightly improved in both intervention and control groups There was no difference in manual dexterity (NHPT score) in both intervention and control groups Both participants and therapists were satisfied with the telerehabilitation system	The home-based telerehabilitation system – the Home Care Activity Desk was as feasible as usual care in terms of clinical outcomes.

TABLE I.—*Continues from previous page.*

Study Author, year, country	Objectives	Study type, participants number (N.)
Motl (2011) [24] USA	To examine the effect of an Internet intervention based on social cognitive theory for favourably increasing physical activity among pwMS	RCT, parallel group, with wait-list control N.=54: intervention group =27 and control group =27 Assessment time points: baseline, postintervention
Paul (2004) [25] Scotland	To explore the effectiveness and participant experience of web-based physiotherapy for people moderately affected with MS	RCT, parallel group N = 30: intervention group = 5 and control = 15 Assessment time points: Baseline, post-intervention
Pilutti (2014) [26] USA	To examine the efficacy of an Internet-delivered, behavioural intervention for improving outcomes of fatigue, depression, anxiety, pain, sleep quality, and HRQOL	RCT, parallel group with wait-list controls N = 82: intervention group = 41 and control = 41 Assessment time points: Baseline, post-intervention
Sandroff (2014) [27] USA	To examined the effect of a physical activity behavioural intervention on cognitive and walking performance	RCT, parallel group with wait-list controls N = 82: intervention group = 41 and control = 41 Assessment time points: Baseline, post-intervention Demographics characteristics (presented based on the level of disability - stratified PDSS scores)

EDSS: Expanded Disability Status Scale; ES: effect size; Activity Questionnaire; ITT: INtention to treat; MS: multiple sclerosis; N: total number; PDDS: patient determined disease steps; pwMS: persons with MS: QoL: quality of life; RCT: randomised controlled trial; RRMS: remitting relapsing MS; SD: standard deviation.

Demographic characteristics	Summary of results	Author's conclusions
Intervention group: mean age:46.1 years (SD 10.4), 90% female; mean disease duration: 8.1 years (SD 6.5); mean Determined Disease Steps Scale score (disease severity): 2.0 (SD 1.8) Control group: mean age 45.6 (SD 9.2), 88% female, mean disease duration: 7.3 (SD 6.2), mean Determined Disease Steps Scale score (disease severity):2.1 (1.9)	Participants in Internet intervention group showed statistically significant and large increase in self-reported physical activity over a 3-month period, whereas the waitlist control condition was associated with a lack of change in physical activity behaviour. There was a reduction in self-efficacy over time in both the intervention and control groups, but the change was unrelated with change in physical activity, indicating that intervention was successful for increasing self-reported physical activity, despite the reduction in self-efficacy over time. The effect of the intervention was mediated through a change in goal setting behaviour, and was most successful in those who did not initially engage in goal setting behaviour and those who had less severe disability.	The internet intervention resulted in a statistically significant and large increase in self-reported physical activity over a 3-month period.
Intervention group: mean age 50.8 years (SD 7.4), 80% female; mean disease duration 12.5 years (SD 7.1), mean EDSS 6. 0 (SD 0.5) Control group: mean age 52.5 years (SD 14.3), 80% female; mean disease duration 12.8 years (SD 10.9), mean EDSS 5.8 (SD 0.5)	There was no statistically significant difference in timed 25ft walk in the intervention group (P=0.170), or other secondary outcome measures, except the Multiple Sclerosis Impact Scale. Effect sizes were generally small to moderate. Participants reported that website was easy to use, convenient, and motivating and would be happy to use in the future.	Web-based physiotherapy is a feasible method and acceptable to people moderately affected with MS.
Intervention group: mean age 48.4 years (SD: 9.1 years), 73.2% female, mean time since diagnosis 10.6 years (SD: 7.1 years), RRMS 75.6%, PDSS: median 2.0 (IQR 4, 0) Control group: mean age 49.5 years (SD: 9.2 years), 78% female, mean time since diagnosis 13.0 years (SD: 9.1 years), RRMS 83%, PDSS: median 3.0 (IQR 3, 0)	Intervention group demonstrated improved fatigue severity and its physical impact, depression and anxiety There were non-significant improvements in pain, sleep quality and physical HRQOL There was significant increase in self-reported physical activity Satisfaction with telecare was high and most patients would recommend this service to others.	Behavioural interventions targeting lifestyle physical activity can be an alternative approach for managing symptoms in MS. (This study is one of a series of studies conducted earlier (Dlugonski 2012 and Motl 2011) and evaluated the same cohort of participants from single database for similar intervention)
Intervention group: PDDS (0-2, N = 18) - Mean age 45.4 years (SD: 10.1 years), 66.7% female, mean time since diagnosis 9.0 years (SD: 7.2 years), RRMS 94.4% PDSS (3-6, N = 19) - Mean age 52.1 years (SD: 6.4 years), 78.9% female, mean time since diagnosis 12.3 years (SD: 6.3 years), RRMS 57.9% Control group: PDDS (0-2, N = 18) - Mean age 49.0 years (SD: 10.0 years), 83.3% female, mean time since diagnosis 12.7 years (SD: 9.7 years), RRMS 94.4% PDDS (3-6, N = 21) - Mean age 51.6 years (SD: 6.7 years), 71.4% female, mean time since diagnosis 14.0 years (SD: 9.0 years), RRMS 71.4%	Intervention group demonstrated a clinically meaningful improvement in cognition and an increase in 6MW distance relative to those in the control group.	The study supports physical activity as a promising tool for managing cognitive impairment and impaired walking performance in pwMS and suggests that physical activity might have specific effects on cognition and non-specific effects on walking performance in this population. (This study is the second report of another study conducted earlier – Pilutti *et al.* 2014)

TABLE II.—*Summary of outcome assessed in the included studies.*

Study	Outcome assessed*			
	Function	Impairment	Participation	Others
Dlugonski (2012) [20]	GLTEQ, MSWS-12	—	MSIS-29	PDDS, SATISFACTION
Egner (2003) [17]	—	FSS	QWB, CES-D	—
Finlayson (2011) [21]	—	FIS, FSS	SF-36	ECQ, PDDS
Frevel (2014) [22]	BBS, DGI, TUG, 2MWT	MFIS	HAQUAMAS	Muscle strength
Gutíerrez (2013) [23]	SOT, MCT, BBS, TS	—	—	—
Huijgen (2008) [11]	ARAT, NHPT	—	—	VAS satisfaction survey
Motl (2011) [24]	GLTEQ, LL-FDI, EXCE, MOEES	—	—	EGS, PDSS
Paul (2014) [25]	25 FWT, BBS, TUG	MS related symptom check list	MSIS, LMSQOL, HADS	—
Pilutti (2014) [26]	GLTEQ	MFIS, FSS, MPQ, PSQI	MSIS-29, HADS	PDDS
Sandroff (2014) [27]	6MWT, IPAQ	—	SDMT	PDDS

*Categorised according to the International Classification of Functioning, Disability and Health (ICF); ARAT: Action Research Arm Test; BBS: Berg Balance Scale; CDP: Computerized Dynamic Posturography; CES: Composite Equilibrium Score; CES-D: Center for Epidemiologic Studies Depression Scale; DGI: Dynamic gait Index; ECQ: Energy Conservation Questionnaire; EDSS: Expanded Disability Status Scale; EGS: Exercise Goal setting Scale; EXSE: Exercise Self-Efficacy Scale; FIS: Fatigue Impact Scale; FSS: Fatigue Severity Score; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAQUAMS: Hamburg Quality of Life Questionnaire in Multiple Sclerosis; IPAQ: International Physical Activity Questionnaire; LMSQOLS: Leeds Multiple Sclerosis Quality of Life Scale; LL-FDI: Late-Life Function and Disability Instrument; MCT: Motor Control Test; MOEES: Multidimensional Outcomes Expectations for Exercise Scale; MPQ: McGill Pain Questionnaire; MSIS-29: Multiple Sclerosis Impact Scale; MSWS-12: Multiple Sclerosis Walking Scale–12; NHPT: Nine Hole Peg Test; PARQ: Physical Activity Readiness Questionnaire; PDDS: Patient Determined Disease Steps; PSQI: Pittsburgh Sleep Quality Index; QWB: Quality of Well- Being Scale; SDMT: Symbol Digit Modalities Test; SF-36: 36-Item Short Form Health Survey; SOT: Sensory Organisation Test; TS: Tinetti Scale; TUG: Timed Up and Go; VAS: Visual Analogue Scale; 6MWT: 6 minute walk test; 25FWT: 25 Foot Walk Test.

were conducted in different countries: 5 in the United States;[18, 21, 22, 25, 27] one each in Spain,[24] Germany [23] and the United Kingdom,[26] while one was a multicenter study conducted in three different countries (Italy, Spain and Belgium).[11] Three studies were conducted by the same group of authors in the same setting and with the same cohort of participants recruited from a single database,[21, 25, 27] of which one reported different outcomes in two different articles.[27]

Sample characteristics

The studies involved a total of 531 participants (277 participants in the treatment groups and 254 in the control groups), with number of participants ranging from 27 to 190 (median 45). Participants were predominantly women, with their proportion ranging from 56% to 87% (mean 74%). The mean age of participants varied from 41 to 52 years (mean 46.5 years) and mean years since diagnosis from 7.7 to 19 years (mean 12.3 years). The majority of participants had a relapsing-remitting course of MS (RRMS). Participants' detailed information, including inclusion/exclusion criteria and baseline demographics, are listed in the Table I.

Interventions

The telerehabilitation interventions evaluated in the included studies varied. Most interventions included physical activity as one of the main intervention components, followed by education and behavioural training. The duration and intensity of the interventions also varied significantly depending on the nature of the intervention, and ranged from one to six months (median 12 weeks). None of the studies reported the recruitment time period. The follow-up periods varied between trials, but all studies assessed the participants immediately after intervention. Only one trial reported long-term follow-up of up to 24 months.[18] The included studies used a broad range of outcome measures (see Table II for a list of outcome measure used). Detailed information about interventions in the included studies is presented in Table III.

Methodological quality of the studies

Methodological quality of the 9 included studies (one with two reports) was rated as 'low' due to substantial flaws in their design with various biases

TABLE III.—*Summary of telerehabilitation interventions.*

Study	Telerehabilitation interventions			
	Contents	Settings	Technology	Duration/intensity
Dlugonski (2012) [20]	Same as Motl 2011 (see below)	Participants' home	Internet-delivered	12 weeks, same as Motl 2011 (see below)
Egner (2003) [17]	Structured in-home education and counselling session delivered by a rehabilitation nurse, which included individual rehabilitation education sessions	Participants' home	Telephone or video	30 to 40 minutes, weekly for 5 weeks, then once every 2 weeks for 1 month.
Finlayson (2011) [21]	Group-based fatigue management program, facilitated by a licensed occupational therapist	Rehab centre	Teleconference	70-minute weekly for 6 weeks
Frevel (2014) [22]	Training programme: balance, postural control exercises and strength training with additional interactive sessions	Participants' home	Internet-delivered	2 training sessions/(45 minutes) weekly for 12 weeks
Gutíerrez (2013) [23]	Monitored telerehabilitation programme, which included gaming protocol, proposing activities that involve integrating proprioceptive, visual, and vestibular sensory information. Experimental group attended at home	Participants' home	Virtual reality system via video-conference using the Xbox 360 and Kinect console	40 sessions, 4 sessions per week (20 minutes per session)
Huijgen (2008) [11]	Home Care Activity Desk (HCAD) – a telerehabilitation intervention for arm/hand function and additional features for videoconferencing and recording. HCAD system	Participants' home	Virtual telerehabilitation programme and video-conference, comprising a hospital-based server and portable unit installed at participant's home	1 month of usual care followed by HCAD- 1 session (30 minutes)/day for 5 days per week for 1 month
Motl (2011) [24]	Social cognitive theory based behavioural intervention that was supplemented with seven one-on-one web-based video coaching interactive sessions (5-10 minutes) using webcam	Participants' home	Internet-delivered	12 weeks (4 in the first month, 2 in second month and 1 in third month)
Paul (2014) [25]	Individualised physiotherapy programme consisting of exercise page containing a video and text explaining the exercise, an audio description of the exercise and a timer	Participants' home	Internet-delivered	Twice per week for 12 weeks
Pilutti (2014) [26]	Same as in Motl 2011 (see above), in addition, participant wore a Yamax SW-401 Digiwalker pedometer, completed a log book and used Goal Tracker software, and received a webcam, and website information	Participants' home	Internet-delivered	15 scheduled one-on-one video coaching sessions for 6 months
Sandroff (2014) [27]	Same as in Motl 2011, Pilutti 2014 (see above). In addition, website materials were delivered in a titrated manner over the 6-month period such that new content became available 7 times during the first 2-month period, 4 times during the second 2-month period, and twice during the final 2 months of the intervention.	Participants' home	Internet-delivered	Weekly one-on-one behavioural coaching sessions via Skype (15 scheduled sessions) for 6 months

observed. These included a lack of proper randomisation, problems with allocation concealment and a lack of blinding. Further, there was also insufficient information about specific methodological issues (Table IV). All studies except one were single-centre trials, with fairly small participant numbers, and a concomitant risk of type I and II errors. The evidence is heterogeneous, particularly in terms of

TABLE IV.—*Levels of quality of individual studies (GRADE* approach).*

Study	Random sequence	Allocation concealment	Blinding of participants / personnel	Blinding outcome assessments	Incomplete outcome data	Selective reporting	Other bias	Study quality rating*
Dlugonski (2012) [20]	?	–	–	–	+	+	?	Low
Egner (2003) [17]	?	?	–	–	+	+	?	Low
Finlayson (2011) [21]	+	+	?	–	–	+	?	Low
Frevel (2014) [22]	+	+	–	–	+	+	?	Low
Gutíerrez (2013) [23]	–	–	–	+	+	+	–	Low
Huijgen (2008) [11]	?	–	–	–	?	+	?	Low
Motl (2011) [24]	?	–	–	–	?	+	+	Low
Paul (2014) [25]	+	–	–	–	+	+	?	Low
Pilutti (2014) [26]	?	–	–	–	+	+	?	Low
Sandroff (2014) [27]	?	?	–	–	+	+	?	Low

*GRADE: Grades of Recommendation, Assessment, Development and Evaluation. '+' = yes; '–' = no; '?' = unclear.

interventions (technology employed, rehabilitation components within the intervention, duration and intensity of the intervention etc.), and diverse outcome measures used.

Summary of main findings

This review of nine RCTs (one with two reports), evaluated a wide range of telerehabilitation interventions, which were complex, using more than one active rehabilitation component which differed in many aspects, including intervention goals, number and extent of the intervention components, duration and intensity, and mode of delivery. Control interventions also differed between studies ranging from "usual care" or "wait-list" to active intervention (such as hippotherapy [23]). The included trials were heterogeneous in terms of outcome measures used and study quality. The quality of evidence is further compromised by the limited number of studies, heterogeneity and the methodological weaknesses identified (underpowered with small sample sizes, high risk of bias, short follow-up periods, lack of rigorous methodology and different outcome measures) amongst the included trials. Quantitative synthesis was therefore not possible. A qualitative synthesis of "best evidence" for telerehabilitation interventions indicates "low" level evidence for:

— short-term benefit in improving functional activities, such as physical activity, balance capacity and postural control compared with baseline, and some benefit in improving walking, physical activity;

— short-term benefit in reducing and/or improving impairments (such as fatigue), and longer-term benefits in improving symptoms such as fatigue, pain and insomnia;

— longer-term improvement in participation, such as improving psychological outcomes and quality of life (QoL).

There is a "very low" level of evidence for participants' and therapists' satisfaction with the telerehabilitation interventions. Subgroup analysis for type of telerehabilitation intervention was not possible due to lack of data. There were no data for the cost effectiveness of telerehabilitation interventions, their impact on health service utilisation (hospitalisation or attendance/access to the health services) and carer burden or social integration (in the form of return to work, study etc.). There were no reports of serious adverse effects attributable to telerehabilitation. A summary of the findings of the included trials is presented based on primary and secondary outcomes categorised according to the International Classification of Functioning, Disability and Health (ICF) [29] framework in Table V.

Discussion

This review investigated the effectiveness of different forms of organised telerehabilitation approaches in adults with MS on measures of activities (and, impairments) and participation, and also of safety and cost effectiveness of these interventions. There was marked heterogeneity between the included 9 RCTs in terms of characteristics, type and mode of delivery of the telerehabilitation interventions, measurement

TABLE V.—*Summary of findings.*

Outcomes	N. of participants (studies)	Effect of telerehabilitation interventions for people with multiple sclerosis	Quality of the evidence (GRADE)#
Change in functional activity (disability)			
Change in disability directly post-intervention Measures: GLTEQ, DGI, BBS, ARAT, NHPT, 25FWT, CES, VPR Follow-up: depended on the type of intervention; range from (1 month – 12 weeks)	232 (intervention group = 122) (6 studies)	Two studies (N.=99) [20, 24] with same cohort of participants showed significant improvement in physical activity in the treatment group at postintervention assessment as measured by GLTEQ (P<0.01). Weekly step count (pedometer) increased significantly in the treatment group at post-intervention assessment (P<0.001). One study (N.=18) [22] showed significant improvement in dynamic and static balance capacity compared to baseline values in both intervention group (e-training) (DGI: P=0.016, BBS: P=0.011) and control (hippotherapy) group (DGI: P=0.011, BBS: P=0.011). There was no difference between groups. One study (N.=35) [11] showed no statistically significant differences between intervention and control groups in arm function as measured by ARAT (mean change 1.26, 90% CI -1.90 to 4.42) and NHPT (mean change 7.24, 90% CI -6.55 to 23.25). One study (N.=30) [25] showed that gait speed measured using 25FWT increased in the intervention group compared to the control group but this was not statistically significant (P=0.170); and the intervention group showed a statistically significant improvement in the physical subscale of the MSIS (P=0.048). One study (N.=50) [23] showed improvements in balance and postural control, with a significant increase in CES of the intervention group (mean change; 8.21 points, P<0.001), but no significant improvement in the control group (mean change: 1.93, P=0.123). Visual Preference Ratio (VPR) and the contribution of vestibular information (Vestibular Ratio) improved significantly in the intervention group (P<0.001), but not in the control group (P>0.05). There were significant post-treatment differences between treatment and control groups in the CES (F=37.873, P<0.001) and the VPR (F=12.156, P<0.001). Significant post-treatment differences between groups were also found for the ability to accept incorrect visual information expressed by the visual conflict parameter (F=15.05, P<0.000). There were no significant between-group differences in the contribution of the visual system (F=2.64, P=0.11) or use of somatosensory information (F=0.117, P=0.734) in the maintenance of balance and stability.	Low
Change in short-term disability 3 months or less after the start of the intervention Measures: GLTEQ Follow-up: up to 3 months	45 (intervention group = 22) (1 study)	One study (N.=45) [20] reported that the treatment group showed a significant increase in physical activity at 3-month follow-up compared to the control group as measured by GLTEQ (P<0.001). There was a non-significant change in assessment scores from post-intervention to 3-month follow-up (P.=0.61).	Low
Change in long-term disability more than 3 months after the intervention Measure:6MWT Follow-up: 6 months-2 years	82 (intervention group = 41) (1 study with 2 reports)	One study with 2 reports (N.=82) [26] showed a significant and positive effect of the intervention on increase in 6MWT distance relative to those in the control group (P=0.07). Physical activity increased most in those with mild disability in the intervention group.	Low
Change in symptoms or impairments			
Change in impairments directly postintervention Measures: FIS, FSS, MFIS, MS Symptom Checklist Follow-up: depended on the type of intervention; range from (1 month-12 weeks)	265 (intervention group = 138) (4 studies)	One study (N.=190) [21] showed a significant reduction in fatigue in intervention group compared to a wait-list control group immediately after intervention as measured by FIS sub-scales (mean [SD]: cognitive -3.12 [6.1], P=0.001; physical -2.53 [6.4], P=0.014; social -6.01 [12.1], P=0.002). One study (N.=27) [17] reported similar fatigue scores (measured using FSS) for all 3 groups (video, telephone and standard care) at 9 weeks post-intervention; however the video group had significantly lower scores than the other 2 groups at month 6 (P<0.05; telephone: SE=0.478; standard care: SE=0.536) and month 18 (P<0.05; telephone: SE=0.569; standard care: SE=0.624). One study (N.=18) [22] reported that fatigue improved significantly in the control (hippotherapy) group (P<0.05 for all MFIS subscales); while the e-training group improved only on the MFIS cognitive subscale (P=0.031). A significant difference between the groups was noted only in the cognitive subscale of the MFIS (P=0.012). One study (N.=30) [25] reported no improvements in symptoms as measured by MS Symptom Checklist.	Low
Change in short-term impairments 3 months or less after the start of the intervention Measures: FIS Follow-up: up to 3 months	190 (intervention group = 94) (1 study)	One study (N.=190) [21] showed a reduction in fatigue at 3 months with large effect size as measured by FIS subscales (ES [95% CI]: cognitive 0.58 [0.48 to 0.68]; physical 0.68 [0.55 to 0.82]; social 0.65 [0.53 to 0.77] and FSS scores: -0.38 [-0.45 to -0.31]).	Low

Table V.—*Continues from previous page.*

Outcomes	N. of participants (studies)	Effect of telerehabilitation interventions for people with multiple sclerosis	Quality of the evidence (GRADE)#
Change in long-term impairments more than 3 months after the intervention Measures: FIS, FSS Follow-up: 6 months-2 years	299 (intervention group = 155) (3 studies)	One study (N.=27) [17] showed a reduction of fatigue measured by FSS in those using video telerehabilitation compared with those using telephone telerehabilitation or standard care groups at 6 months (P<0.05; telephone: SE=0.478; standard care: SE=0.536) and 18 months (P<0.05; telephone: SE=0.569; standard care: SE=0.624). At 12 months follow-up, there was a significant difference in fatigue scores between the video and standard care groups (P<0.05; SE=0.471). One study with 2 reports (N.=82) [26] showed a significant and positive effect of the intervention on fatigue severity (FSS, P=0.001) and its physical impact (FIS, P=0.008) at 6-month postintervention. The results also indicated a favourable effect of the intervention on symptoms of pain (MPQ, P=0.0.08) and sleep quality post-trial (PSQI, P=0.06), although the differences between groups did not reach statistical significance. One study (N.=190) [21] showed reduction in fatigue at 6 months with a large effect size as measured by FIS subscales (ES [95% CI]: cognitive 0.55 [0.46 to 0.64]; physical 0.61 [0.50 to 0.72]; social 0.67 [0.58 to 0.76] and FSS score: -0.33 [-0.36 to -0.30]).	Low
Change in participation			
Change in psychological outcomes Measures:CES-D, HADS, SDMT Follow-up: variable (range 1 month-2 years)	139 (intervention group = 76) (3 studies)	One study (N.=27) [17] showed no significant difference in depressive symptoms measured by CES-D at end of the intervention period (9 weeks). Mean depression scores were lower in those receiving telerehabilitation by video compared with telephone and standard care group symptoms decreased at 6, 8 and 24 months follow-up. Being male was a significant predictor for an increased depression score at every measurement point except at 24 months (P<0.05). Mean CES-D scores fluctuated throughout each measurement point for all groups, but seemed to decrease at 24 months in all 3 groups, but not statistically significant. Mean depression scores were lower in those receiving telerehabilitation by video compared to telephone and standard care groups and depressive symptoms also decreased at the 6-, 8- and 24-month follow-ups, but this was not significantly different between groups. One study (N.=30) [25] reported a small non-significant improvement in anxiety measured by HADS in the control group compared with the treatment group at post-treatment (8-9 weeks) (P=0.016). One study with two reports (N.=82) [26] showed a statistically significant group interaction in psychological outcomes on SDMT scores (F=5.68, P=0.02), which was moderate in magnitude (partial eta squared [η_2]=0.08). There was a clinically meaningful improvement in SDMT scores in the subgroup with mild disability in the intervention condition (~6 points increase, moderate effect size [d]=0.41), whereas those with moderate disability in the intervention condition demonstrated minimal change (~1 point decrease, [d]=0.12). There were minimal changes in SDMT scores for those with both mild and moderate disability (~1 point increase, [d]=0.10 for both) in the control group. There was also significant improvement in depression and anxiety in the intervention group (with large effect size [η_2]=0.10 for both) compared with the control group measured by the HADS (depression: F=7.90, P=0.006; anxiety: F=8.00, P=0.006).	Low
Change in quality of life Measures: QWB, HAQUAMS, MSIS-29, SF-36, LMSQOLS, Follow-up: variable (range 1 month–2 years)	392 (intervention group = 201) (6 studies, 1 with 2 reports)	One study (N.=27) [17] reported no significant difference in QoL measured using QWB at the end of the intervention period (9 weeks). Mean QWB scores for each measurement point (6, 9, 12, 18 and 24 months) were higher (indicating higher QoL) for those in the video group than for the standard care and telephone groups, but were significantly better in the video group compared to the telephone group at month 12 only (P<0.05; SE=0.023). The telephone group and standard care groups reported similar mean QWB scores over the 2-year follow-up period. One study (N.=18) [22] showed significant improvement in QoL measured by HAQUAMS (cognition: P=0.026; function of lower limb: P=0.008; mood: P=0.045) in the control group (hippotherapy), but not in the intervention group (e-training). One study (N.=45) [20] showed non-significant condition-by-time interactions for QoL measured by MSIS-29. There was no significant correlation between changes in QoL from base line to post-intervention in either the treatment or control groups. One study (N.=190) [21] showed that significant improvement in HRQoL in the intervention group on the SF-36 subscales except the physical functioning and bodily pain subscales: change score (95% CI): vitality 6.99 (4.29 to 9.69); role emotion 10.08 (4.13 to 16.04); mental health 5.78 (3.89 to 7.67); social function 7.95 (4.09 to 11.82); general health 3.61 (1.37 to 5.85); role physical 11.12 (6.22 to 16.02). One study (N.=30) [25] reported non-significant improvement in HRQoL measured by LMSQOLS in the treatment group compared with control group post-treatment (8-9 weeks) (mean difference -0.07 vs. 1). One study with 2 reports (N.=82) [26] reported that participants in the intervention group perceived a positive change in physical HRQoL measured by MSIS-29 (P=0.06).	Low

TABLE V.—*Continues from previous page.*

Outcomes	N. of participants (studies)	Effect of telerehabilitation interventions for people with multiple sclerosis	Quality of the evidence (GRADE)#
Change in other outcomes			
Cost effectiveness	531 (intervention group = 277) (9 studies)	Not measured in any of the studies	See "Impact"
Process evaluation (user satisfaction) Measures: Self-designed Likert scale, VAS scale Follow-up: variable (range 1-3 months)	80 (intervention group =46) (2 studies)	One study (N.=45) [20] showed that participants were most satisfied with (mean±SD): the overall programme: 4.8±0.4, staff: 4.9±0.2 and pedometer: 4.7±0.6, but slightly less satisfied with the website itself: 4.1±0.9. One study (N.=35) [11] reported that overall, both participants and therapists were satisfied with the intervention (over 55% in all 6 items). Both participants and therapists were less satisfied with the aesthetic aspect of the system and had difficulty completing tasks.	Very low
Serious adverse events	531 (intervention group = 277) (9 studies)	No serious adverse events reported.	See "Impact"
Caregivers-related outcomes	531 (intervention group = 277) (9 studies)	Not measured in any of the studies.	See "Impact"

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
high quality: further research is very unlikely to change our confidence in the estimate of effect.
moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
very low quality: we are very uncertain about the estimate.
ARAT: Action Research Arm Test; CES: Composite Equilibrium Score; CES-D: Center for Epidemiologic Studies Depression Scale; CI: Confidence interval; DGI: Dynamic Gait Index; EDSS: Expanded Disability Status Scale; ES: Effect size; FIS: Fatigue Impact Scale; FSS: Fatigue Severity Score; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAQUAMS: Hamburg QoL Questionnaire in MS; HRQoL: Health related quality of life; IQR: inter quartile range; LMSQOLS: Leeds MS Quality of Life Scale; MPQ: McGill Pain Questionnaire; MS: Multiple Sclerosis; MSIS-29: MS Impact Scale; NHPT: Nine Hole Peg Test; PSQI: Pittsburg Sleep Quality Index; QoL: Quality of life; QWB: Quality of Well- Being Scale; SD: Standard deviation; SDMT: Symbol Digit Modalities Test; SE: Standard Error; SF-36: 36-Item Short Form Health Survey; SOT: Sensory Organisation Test; VPR: Visual Preference Ratio; 6MWT: 6 Meters Walk Test; 25FWT: 25 Foot Walk Test; 95% CI: 95 percent confidence interval.

tools used (even for identical outcomes), treatment and control protocols, and length of follow-up. Pooling data for meta-analyses to make meaningful statements for both primary and secondary outcomes was not possible, therefore a best-evidence synthesis was performed using a qualitative analysis. Overall, this review indicates that telerehabilitation has some impact on improving function and symptoms (including cognitive function), but does not have an appreciable impact on disease-specific QoL in pwMS. There are no cost data or process measures data (such as hospitalisation or access to services).

This review highlighted a number of limitations in the studies evaluating telerehabilitation interventions. The methodological quality of the included studies was 'low' due to substantial flaws in their methodological design with various biases observed. In addition, adequate descriptions of the content of telerehabilitation programmes are often lacking. Difficulties in assimilation of data are further compounded by the diversity of outcome measures and follow-up periods. Key areas such as cost-effectiveness of telerehabilitation, carers' issues, lack of longer-term follow-up and neuropsychological sequelae following MS (such as mood and work-related issues) have yet to be addressed. The generalisability and applicability of results are limited, as most studies recruited participants from a single centre with strict inclusion and exclusion criteria. Moreover, generalisability of results to different countries and healthcare systems is challenging, as studies were conducted predominantly in the USA and Europe.

This review found various limitations and gaps in knowledge, which could suggest directions for future research. These include, but are not limited to:

— more methodologically robust studies, *e.g.*, RCTs comparing different models and intensity of telerehabilitation;

— large-scale systematic and 'practice-based trials' in which data are routinely gathered without disrupting the natural milieu of treatment to provide valuable information about outcomes in real-life clinical settings;

— use of more sensitive and appropriate validated outcome measures that are important for patients and their representatives and that focus on impairments, activity limitations and restriction in participation;

— longitudinal data population for longer-term care needs;

— carer perspectives and their involvement in telerehabilitation;

— research about specific telerehabilitation modalities and to improve evidence-based practices;

— cost effectiveness of telerehabilitation;

— more emphasis on participatory domains (cognitive outcomes and QoL) for impact on societal integration.

Future studies in telerehabilitation should focus on improving the methodological and scientific rigour of clinical trials, with larger sample sizes and with longer-term follow-up. Further, active clinician involvement is needed to build evidence in this area for everyday clinical practice.

Conclusions

This review highlights the lack of robust, methodologically-strong studies evaluating the effectiveness of telerehabilitation intervention in pwMS. Overall, the review found "low" quality evidence for a beneficial effect of telerehabilitation intervention on reducing short-term disability (and impairments, such as fatigue). There was also 'low' quality evidence suggesting some benefit in improving functional activities (and impairments) in the longer-term, and improving psychological outcomes and QoL. There are limited data on process evaluation (participants' and therapist satisfaction) and, surprisingly, none of the studies addressed cost effectiveness. Telerehabilitation has a major role in providing remote rehabilitation to people with chronic neurological conditions in the future, and has potential to fill the existing service gap in the care of pwMS. However, clinical applicability of the findings of this review and the effectiveness of telerehabilitation interventions need to be confirmed in future research.

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