National Institute for Health and Care Excellence

Draft for consultation

Rehabilitation for chronic neurological disorders including acquired brain injury

[J] Evidence review for fatigue management

NICE guideline <number>

Evidence reviews underpinning recommendations 1.14.3, 1.15.1 to 1.15.7 and research recommendations in the NICE guideline

April 2025

Draft for consultation

This evidence review was developed by NICE

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Fatigue Management

Review question

What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Introduction

Fatigue is common in people with chronic neurological conditions, including people who have experienced a traumatic brain injury, and it is important to address this symptom effectively. The causes of fatigue are typically varied and poorly understood, and levels of fatigue can often fluctuate, with an often-prolonged recovery period after an episode of severe fatigue. Fatigue can have a very significant adverse impact on an individual's ability and quality of life and can cause disruptions to activities of daily living, the ability to take part in social life or to work, and mood levels. It can also be associated with cognitive impairment which further limits participation and integration and can also lead to increased disability, poorer general health. These impacts may in turn necessitate greater use of health and social care resources.

This review sought to determine the effectiveness of multi modal (combined physical and psychological) rehabilitation to address fatigue.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults and children with rehabilitation needs due to the following chronic neurological disorders: ○ Acquired brain injury ○ Acquired spinal cord injury ○ Acquired peripheral nerve disorders ○ Progressive neurological diseases ○ Functional neurological disorders
Intervention	• Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Comparison	Interventions compared with others in the same group or: • Uni-modal rehabilitation for fatigue management (physical or psychological interventions) • Placebo (placebo or sham) • Control (no intervention, waitlist, standard rehabilitation care alone, or 'usual care') • The same intervention (as listed under 'intervention') but varied in terms of: ○ Frequency ○ Intensity ○ Timing ○ Setting
Outcomes	**Critical** • Fatigue severity or impact on fatigue (assessed using a validated, global, patient-reported measure of fatigue such as the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Fatigue Impact Scale (FIS), the

	Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F) and the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PEDS-QL MFS)

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (Supplement 1: methods).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Ten randomised controlled trials (RCTs) were included in this review: Carter 2014; Hersche 2019; Louie 2022; Nguyen 2017; Patt 2023; Rietberg 2014; Ryan 2020; Rytter 2019; Thomas 2017; Veenhuizen 2019.

The included studies are summarised in Table 2.

Three studies were conducted in the UK (Carter 2014; Ryan 2020; Thomas 2017); 2 studies were conducted in Switzerland (Hersche 2019; Patt 2023); 2 studies were conducted in Australia (Louie 2022; Nguyen 2017); 2 studies were conducted in the Netherlands (Rietberg 2014; Veenhuizen 2019); and 1 study was conducted in Denmark (Rytter 2019).

Ten studies investigated multi modal (combined physical and psychological) rehabilitation interventions for fatigue management; 8 of these were in people with progressive neurological disorders (Carter 2014; Hersche 2019; Louie 2022; Patt 2023; Rietberg 2014; Ryan 2020; Thomas 2017; Veenhuizen 2019), and 2 studies were in people with acquired brain injury (Nguyen 2017; Rytter 2019).

There were no trials reporting data for interventions on fatigue management for children and young people with a chronic neurological disorder. Additionally, none of the included studies reported data from adults with an acquired spinal cord injury, acquired peripheral nerve disorder or a functional neurological disorder.

Data for the following outcome was identified through analysis of the included studies:

- Fatigue

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes
Carter	N=120 adults with multiple sclerosis	EXIMS	Usual care for example, continued to	• Fatigue severity or

Study	Population	Intervention	Comparison	Outcomes
2014 RCT UK	• EXercise Intervention for people with MS (EXIMS) programme plus usual care: n=60 • Usual care: n=60 Age in years [Mean (SD)]: • EXIMS: 45.7 (9.1) • Usual care: 46.0 (8.4) Sex (M/F): • EXIMS: n=17/n=43 • Usual care: n=17/n=43 Chronic neurological disorder category: progressive neurological disease	12-week programme with supervised exercise sessions incorporated cognitive-behavioural techniques to promote long-term participation in physical activity. Weeks 1-6: 2x 1-hour (maximum) supervised sessions at the centre and 1 self-directed exercise session at home every week. Weeks 7-12: 1 supervised session at the centre and 2 self-directed exercise sessions at home every week. Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.	receive any concomitant care they were already receiving, with no additional treatment. Participants in the usual care group were offered 3 exercise sessions at the university exercise research facility and individual exercise advice after the study.	impact on fatigue
Hersche 2019 RCT Switzerland	N=47 adults with multiple sclerosis • Inpatient energy management education (IEME) + rehabilitation as usual (RAU): n=24 • Progressive muscle relaxation (PMR) + RAU: n=23 Age in years [Mean (SD)]: • IEME + RAU: 51.2 (1.7) • PMR + RAU: 51.8 (2.2) Sex (M/F): • IEME + RAU: n=8/n=16 • PMR + RAU: n=8/n=15 Chronic neurological disorder	IEME + RAU IEME Sessions of 6.5-hours in duration over a 3 week period. The IEME started with 1x 1-hour individual session, followed by 5x 1-hour self-contained IEME group sessions (minimum 2, maximum 7 participants) delivered twice a week, and it concluded with a 0.5-hour individual session. Participants acquired knowledge and understanding about factors that influence energy and the consequences of fatigue on their habits and lifestyle. Subsequently, they identified and implemented	PMR + RAU PMR 6x1-hour face-to-face group sessions (maximum 12 participants) Standardised series of relaxation exercises combined with deep breathing. RAU This individualised program included physiotherapy, occupational therapy, speech therapy, neuropsychological training, and counselling, if relevant. The difficulties due to fatigue were discussed in individual OT sessions but no systematic fatigue	• Fatigue severity or impact on fatigue

Study	Population	Intervention	Comparison	Outcomes
	category: progressive neurological disease	tailored behaviour modification. RAU: same as comparison group. Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.	management education was provided as part of RAU.	
Louie 2022 RCT Australia	N=23 adults with multiple sclerosis • Maximising Abilities, Negotiating and Generating Exercise options (MANAGE) programme: n=12 • Waitlist control: n=11 Age in years [Mean (SD)]: • MANAGE: 48.3 (14.1) • Waitlist control: 8.3 (14.1) Sex (M/F): • MANAGE: n=6/n=6 • Waitlist control: n=4/n=7 Chronic neurological disorder category: progressive neurological disease	MANAGE 12 week self-management programme focusing on education, exercise and community integration, supported by behaviour change techniques 2x 60-minute sessions per week of exercise and 1x 60-minute education sessions per week for first 6 weeks in outpatient clinic; community supported sessions for last 6 weeks. Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.	Waitlist control - continued to receive any concomitant care they were already receiving, with no additional treatment.	• Fatigue severity or impact on fatigue
Nguyen 2017 RCT Australia	N=24 adults with traumatic brain injury • Cognitive behaviour therapy (CBT) + exercise: n=13 • Treatment as usual: n=11 Age in years [Mean (SD)]: • CBT + exercise: 45.53 (13.87)	CBT + exercise 6 CBT modules addressing sleep and fatigue across 8 sessions plus as part of behaviour activation, 3-5x 30-minutes of moderate exercise sessions per week. Duration not reported	Treatment as usual - continued to receive any concomitant care they were already receiving, with no additional treatment.	• Fatigue severity or impact on fatigue

Study	Population	Intervention	Comparison	Outcomes
	• Treatment as usual: 41.90 (12.95) Sex (M/F): • CBT + exercise: n=9/n=4 • Treatment as usual: n=4/n=7 Chronic neurological disorder category: Acquired brain injury	Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.		
Patt 2023 RCT Switzerland	N=106 adults with multiple sclerosis • Inpatient energy management education (IEME) + high-intensity interval training (HIIT): n=53 • Progressive muscle relaxation (PMR) + moderate continuous training (MCT): n=53 Age in years [Mean (SD)]: • IEME + HIIT: 49.98 (10.90) • PMR + MCT: 49.51 (8.81) Sex (M/F): • IEME + HIIT: n=19/n=34 • PMR + MCT: n=16/n=37 Chronic neurological disorder category: progressive neurological diseases	IEME + HIIT IEME Started with a 1:1 individual 1-h session, subsequently, they participated in five 1-h group sessions, and an individual 30-min session over 3 weeks HIIT Five 1.5-min high-intensive intervals twice-weekly for 3 weeks “Booster” was sent to all participants 6 weeks after discharge. Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management	PMR + MCT PMR Six 1-h group sessions over 3 weeks MCT Participants cycled continuously for 24 mins twice-weekly for 3 weeks “Booster” was sent to all participants 6 weeks after discharge.	• Fatigue severity or impact on fatigue
Rietberg 2014 RCT Netherlands	N=50 adults with multiple sclerosis • Multidisciplinary Rehabilitation programme for fatigue: n=25	Multidisciplinary Rehabilitation programme for fatigue 12-week individually tailored multidisciplinary rehabilitation programme.	MS nurse 1-hour session and subsequent follow-up consultation every 3 weeks for 12-weeks	• Fatigue severity or impact on fatigue

Study	Population	Intervention	Comparison	Outcomes
	• Multiple sclerosis (MS) nurse: n=25 Age in years [Mean (SD)]: • Multidisciplinary Rehabilitation programme for fatigue: 45 (9.9) • MS nurse: 47 (8.6) Sex (M/F): • Multidisciplinary Rehabilitation programme for fatigue: n=9/n=14 • MS nurse: n=8/n=17 Chronic neurological disorder category: progressive neurological diseases	2x 45-minute supervised aerobic exercise per week; 1-hour occupational therapy session (with follow-up); 1-hour social work session (with follow-up) Programme focussed on optimising self-management behaviour in daily life activities on the domains of physical fitness, behaviours or cognitions that perpetuate fatigue, and energy conservation Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management	The nurse discussed general principles of planning of activities, priority setting, energy conservation, accepting help from others with daily life activities or use of devices. Physical activity was recommended. Patients were advised on nutrition and alcohol and drug intake.	
Ryan 2020 RCT UK	N=60 adults with multiple sclerosis • i-Step MS + usual care: n=30 • Usual care: n=30 Age in years [Mean (SD)]: • i-Step MS + usual care: 56.9 (9.0) • Usual care: 56.7 (9.2) Sex (M/F): • i-Step MS + usual care: n=13/n=17 • Usual care: n=6/n=24 Chronic neurological disorder category: progressive neurological diseases	i-Step MS + usual care Four physical activity sessions with behaviour change techniques (session 1+3: 45-minutes; sessions 2+4: 30-minutes) over 12 weeks Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management	Usual care - continued to receive any concomitant care they were already receiving, with no additional treatment.	• Fatigue severity or impact on fatigue

Study	Population	Intervention	Comparison	Outcomes
Rytter 2019 RCT Denmark	N=89 adults with persistent post-concussive symptoms • Specialised interdisciplinary rehabilitation (S-rehab): n=45 • Standard care: n=44 Age in years [Mean (SD) not reported] [n, 18–29 years; 30–43 years; >44 years]: • S-rehab: 12;21;12 • Standard care: 12;24;8 Sex (M/F): • S-rehab: n=16/n=29 • Standard care: n=14/n=30 Chronic neurological disorder category: acquired brain injury	S-rehab 22-week interdisciplinary rehabilitation targeting cognitive, emotional and physical domains as well as interpersonal skills within the context of a therapeutic environment Module 1: 12–14 individual consultation sessions with a neuropsychologist (1–2-hours per week), a total of 24-hours of group therapy (2-hours per week) combining psychoeducation, small exercises and group discussions; 33 hours (2–3-hours per week) of individual exercise training and coaching by a physiotherapist. Module 2: 10 individual consultation sessions with a neuropsychologist (1- hour per week), 16 hours of group work (1.5-hour per week), 10.5-hours of individual exercise training and coaching with a physiotherapist (1-hour per week), 1 meeting with a case manager in the participant's municipality and 2 meetings with an existing or potential employer. Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management	Standard care Some participants in the standard care group received no, or a very limited, treatment funded by the municipality, while others received several therapies. Participants in the standard care group were phoned once a month by a project coordinator, who asked them about their general condition and about the treatments they were currently receiving.	• Fatigue severity or impact on fatigue
Thomas 2017 RCT UK	N=30 adults with multiple sclerosis • Mii-vitaliSe + usual care: n=15 • Waitlist control: n=15	Mii-vitaliSe + usual care 20-week Physiotherapist-facilitated Nintendo Wii intervention package that uses commercial software and aims to support people with	Waitlist control - continued to receive any concomitant care they were already receiving from the Dorset MS service, with no additional treatment.	• Fatigue severity or impact on fatigue

Study	Population	Intervention	Comparison	Outcomes
	Age in years [Mean (SD)]: • Mii-vitaliSe + usual care: 50.9 (8.08) • Waitlist control: 47.6 (9.26) Sex (M/F): • Mii-vitaliSe + usual care: n=1/n=14 • Waitlist control: n=2/n=13 Chronic neurological disorder category: progressive neurological diseases	MS to increase their physical activity levels Weekly modules (Week 1 and 2: Orientation to Wii; Week 3: Installation of equipment and commencement of individual programme at home; Week 5: Follow-up; Week 7: Review visit; Week 12: Follow-up; Week 16: Review visit; Week 20 and thereafter: Ongoing support) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management		
Veenhuizen 2019 RCT Netherlands	N=53 adults with neuromuscular disease • Energetic programme: n=29 • Usual care: n=24 Age in years [Mean (SD) not reported] [Median (IQR)]: • Energetic programme: 52 (37-63) • Usual care: 50 (41-60) Sex (M/F): • Energetic programme: n=8/n=21 • Usual care: n=9/n=15 Chronic neurological disorder category: progressive neurological diseases	Energetic programme 16-week Aerobic exercise training, exercise education, ECM, and implementation and relapse prevention programme Aerobic exercise training (3x 30-minute sessions per week for 16 weeks); exercise education (3x 60-minute sessions during the first 3 weeks); ECM (8x 90-minutes sessions spread across the intervention period); implementation and relapse prevention (10 group sessions).	Usual care - continued to receive any concomitant care they were already receiving, with no additional treatment. Participants were not prescribed (or withheld) any specific intervention, which meant that some received physical therapy in primary care, other forms of multidisciplinary rehabilitation care, or no intervention at all.	• Fatigue severity or impact on fatigue

CBT: cognitive behaviour therapy; ECM: energy conservation management; EXIMS: exercise intervention for people with MS; HIIT: high-intensity interval training; IEME: Inpatient energy management education; IQR: interquartile range; MANAGE: maximising abilities, negotiating and generating exercise options; MCT: moderate continuous training; Mii-vitaliSe: physiotherapist-facilitated Nintendo Wii intervention package; MS: multiple sclerosis;

PMR: Progressive muscle relaxation; RAU: rehabilitation as usual; RCT: randomised controlled trial; SD: standard deviation; S-rehab: specialised interdisciplinary rehabilitation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Multi modal (combined physical and psychological) intervention versus unimodal (physical or psychological) intervention

Multi modal inpatient energy management education (IEME) and exercise interventions in adults with multiple sclerosis showed no important differences at all time-points compared with uni modal exercise interventions in terms of fatigue severity, measured using Fatigue Scale for Motor and Cognitive Functions (FSMC) or Modified Fatigue Impact Scale (MFIS).

The quality of the evidence ranged from very low to moderate. Outcomes were typically downgraded due to concerns over risk of bias from the contributing studies.

Multi modal (combined physical and psychological) intervention versus control

A multi modal cognitive behavioural therapy and exercise intervention in adults with persistent post-concussive symptoms showed an important benefit over control in terms of fatigue severity measured using the Brief Fatigue Inventory (BFI) at 4-months, however no important difference was seen in fatigue severity measured using the Fatigue Severity Scale (FSS) at 4-months.

A specialised interdisciplinary rehabilitation intervention in adults with traumatic brain injury showed a statistically significant benefit over control in terms of ‘general fatigue’ and ‘reduced activities’ at 6 months, and ‘mental fatigue’ at post-intervention and 6-months, measured using Multidimensional Fatigue Inventory-20 (MFI-20). The term statistically significant benefit rather than important benefit is used as although there is a statistically significant benefit, we cannot ascertain clinical importance as no standard deviations are available for the data. No statistically significant benefits were seen for ‘physical fatigue’ and ‘reduced motivation’ at post-intervention and 6-months, and ‘general fatigue’ and ‘reduced activities’ at post-intervention, measured using MFI-20.

Overall, multi modal (combined physical and psychological) rehabilitation interventions in adults with multiple sclerosis showed an important benefit over control in terms of fatigue severity at post-intervention and follow-up (ranging from 3-6 months). One study in the multi modal (combined physical and psychological) rehabilitation intervention group that wasn’t included in the meta-analyses, as no overall fatigue score was provided, showed no important differences over control in terms of fatigue severity, measured using Fatigue Symptom inventory (FSI) sub-scales.

The energetic self-management programme in adults with progressive neurological disease showed no important differences at all time-points over control in terms of fatigue severity, measured using Checklist Individual Strength (CIS).

The quality of the evidence ranged from very low to moderate. Outcomes were typically downgraded due to concerns over risk of bias from the contributing studies and imprecision in the effect estimate.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

See supplementary material 2 for details on the economic search undertaken for this guideline.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee prioritised fatigue severity or impact on fatigue as a critical outcome because they wanted to specifically identify interventions focussed on the management of fatigue in people with chronic neurological disorders. Fatigue severity or impact on fatigue levels would therefore be key to demonstrating the effectiveness of the intervention.

The quality of the evidence

The evidence was assessed using GRADE methodology and the overall confidence in the findings ranged from very low to moderate.

Findings were downgraded due to concerns relating to risk of bias (for example, when there was a lack of blinding in a study or if there was a large loss to follow-up) and imprecision (for example, when 95% confidence intervals crossed 1 or more decision-making threshold). No evidence was downgraded for indirectness.

To conduct meta-analyses, outcomes were analysed as standardised mean difference as the majority of outcomes were assessed using different validated and standardised assessment tools. Single study outcomes were also reported as standard mean deviations where possible, so that the outcomes were standardised across the review.

Not all studies were meta-analysed, some studies didn't report fatigue severity or impact on fatigue as an overall score but rather as individual sub-domains. In these circumstances, the individual sub-domains were reported separately rather than meta-analysed with the overall scores.

See appendix F for full GRADE tables with quality ratings of all outcomes.

Benefits and harms

Pain management

The committee discussed the importance of adequate pain management during rehabilitation for people with chronic neurological disorders. While it is not a primary intervention for fatigue, and therefore has not been covered in this evidence review, the committee's experience and expertise shows how central proper analgesia is on the effectiveness of rehabilitation for chronic neurological disorders. Individuals are much less likely to complete rehabilitation programmes if they cause or exacerbate current pain levels. Unmanaged pain levels can also negatively impact physical functioning and emotional wellbeing, which can mask potential benefits of interventions. Therefore, the committee recommended that pain management should be discussed alongside rehabilitation goals and plans. They also highlighted the reciprocal nature of pain management, noting that interventions for fatigue also act to reduce or improve pain.

Fatigue

The committee discussed the importance of identifying fatigue in people with CND, to enable appropriate management because management of fatigue is fundamental in enabling the person to engage in rehabilitation activities and treatments that will improve overall health and wellbeing. The committee emphasised that it is paramount to ask this question each time rehabilitation is discussed as fatigue is common but it isn't always recognised by the healthcare professional or person with CND that there are difficulties, and that management is warranted. In the committee's experience, this question is often overlooked by healthcare professionals and fatigue goes undiagnosed, which can significantly impact the individual's overall health and wellbeing and the ability to engage in rehabilitation. The committee also emphasised that fatigue is not static and can fluctuate for a person with CND. Given the significant impact fatigue can have, the committee recommended that healthcare professionals ask this question to people with CND at initial holistic assessment and subsequent reviews of any rehabilitation activity or treatment.

The committee highlighted that scales to measure fatigue do not always reflect the lived experience, often underestimating the impact of fatigue in people with CND. The committee discussed that assessment of fatigue can be complicated because fatigue impacts on participation in daily activities such as work, school, socialising and physical activity, and in turn participation in daily activities such as work, school, socialising and physical activity impacts on fatigue. Therefore, the committee recommended that healthcare professionals ask the wider question of how fatigue impacts daily activities and how daily activities impact fatigue on the person's best and worst days in order to inform a tailored approach to fatigue management that suits the person's lifestyle and expectations.

The committee discussed the importance of a person with CND's awareness and understanding of their fatigue and its impact. The committee emphasised that an increased awareness and understanding of fatigue and how it affects the person for example what activities worsen or improve fatigue, can lead to better management. However the committee recognised that some people struggle with understanding or accepting that they are being affected by fatigue and the connection between fatigue and their day to day functioning. Therefore, the committee recommended that the person's awareness and understanding of their fatigue and its impact should be taken into account, when assessing and managing fatigue.

The committee discussed the pivotal role of family and carers in identifying the impact fatigue has on different populations of people with CND. The committee highlighted that CYP often have less insight on fatigue or the impact fatigue has on their daily life, most often due to the combination of developmental age and the determination to participate in activities with peers at school, which can lead to the inability to function in the evenings. CYP often lack the capacity to deal with the consequences of fatigue and participation in activities, therefore family and carers are imperative in making decisions such as planned breaks until they have the

autonomy to make those decisions. The committee also discussed that some people with CND (for example, those who have a traumatic brain injury or CYP), may have difficulty expressing that they have fatigue, and family and carers are therefore critical in highlighting the impact fatigue is having. The committee recommended that family and carers are therefore supported in finding out how fatigue impacts on the individual with CND.

The committee discussed the importance of not assuming that fatigue is caused by a CND, as other factors may be contributing to fatigue, which should be considered and managed appropriately. The committee highlighted anxiety, depression, difficulty sleeping, side effects of medicines and illness such as infections, anaemia and thyroid dysfunction, as factors that precipitate fatigue. In view of this, the committee recommended that healthcare professionals look for underlying causes of fatigue and refer for treatment, as necessary.

The committee discussed the 2 meta-analyses conducted in the evidence review that showed an important benefit in fatigue at post-intervention and follow-up (ranging from 3-6 months) in people with MS receiving multi modal (combined physical and psychological) rehabilitation when compared to control. In view of this, the committee agreed that a fatigue management approach should be offered to people with CND.

The committee noted however that the evidence was very low quality and that the multi modal interventions in each study were very different. Furthermore, the majority of studies that weren't meta-analysed failed to show any important differences in overall fatigue. Aside from the meta-analysis, only 1 RCT showed an important benefit in fatigue at 4-months follow-up using the FSS when comparing a multi modal cognitive behaviour therapy and exercise intervention with control. The committee highlighted that the FSS scale used in the study was not validated for use in fatigue secondary to ABI, however the validated BFI scale also used in the study showed no important difference between the intervention and control. Therefore, the committee agreed that it was difficult to recommend a specific multi modal rehabilitation package for fatigue but that the dual elements of some kind of physical activity together with psychological therapy identified in the evidence e.g. pacing, other energy conserving strategies or CBT, were key elements in an effective fatigue management approach in the context of rehabilitation. The committee recommended that health care professionals prioritise what is important to the person and to agree goals related to fatigue management integrated within the overall rehabilitation plan. The committee agreed that the fatigue management approach could include energy conservation strategies, cognitive behavioural therapy, and appropriate physical activity, all of which were elements that were included in the studies that showed benefit over control.

The committee discussed that people with fatigue and CND often have difficulty managing their energy levels. This can look very different in CYP and adults. In CYP, due to their lack of insight and their determination to participate in activities, supporting them may be a more active role such as planning breaks and opting out of activities. Whereas, in adults support to manage energy levels may be discussing competing priorities in how they manage their fatigue for example, how to manage fatigue in balance with activities that individuals with CND like to do. Further highlighting that a person-centric approach should be adopted when planning a fatigue management approach for a person with CND.

Although, the evidence review didn't specifically address physical activity as a uni modal intervention for fatigue management, the committee discussed the importance of physical activity for longer term general health benefits even in the presence of fatigue. The committee highlighted that the type or level of physical activity will not look the same for all people with CND and fatigue, for example high-intensity interval training (HITT) may be appropriate for one person, whereas for another person they may be so fatigued that they are in bed for 3-days unable to function after a session and deterred from any further physical activity. The committee discussed trial and error methods and problem solving on the most appropriate physical activity regimens for the individual with fatigue and CND. In view of this, the

committee recommended that even in the presence of fatigue, for longer term general health benefits, appropriate physical activity should always be encouraged.

The committee were disappointed in the paucity of effectiveness evidence identified for CYP for this review question. This review area is paramount to rehabilitation, as fatigue can be a significantly debilitating aspect of a CND which limits participation in life, education, and leisure. The committee therefore made a research recommendation covering the original question specifically for CYP, with a view to strengthen existing recommendations and informing new recommendation in this area for future guideline updates.

Cost effectiveness and resource use

There was no existing economic evidence in this area.

Pain management is already integral to rehabilitation. Consistently considering pain when discussing and agreeing rehabilitation goals and plans may identify more people needing pain management. However, many existing rehabilitation interventions also can reduce pain or improve pain management, so no significant increase in resource use is anticipated.

The committee explained that people with CND are often seeking help with fatigue. Nevertheless, healthcare professionals often overlook fatigue. Therefore, actively inquiring about fatigue and involving family and carers where needed, for example, where people lack insight into their condition, will ensure that it is not overlooked, potentially leading to more cases being identified and better management.

The committee explained that any standard rehabilitation approach would include fatigue management, such as, conservation strategies, cognitive behavioural techniques, or appropriate physical activity. However, they noted that fatigue is an individualised experience requiring personalised management. Whilst recommendations on fatigue would represent standard care for most services, additional resources may be needed where practices are sub-optimal, and fatigue is currently overlooked or not discussed with people with CND and their families and carers.

The committee was also aware that only small changes in practice as a result of these recommendations may have a significant impact on NHS resources due to the large population needing rehabilitation in relation to a chronic neurological disorder and fatigue symptoms. However, fatigue management for most people includes relatively low-cost approaches such as advice on pacing, breaks, general physical exercise and building self-awareness. The committee also discussed that fatigue significantly impacts health and wellbeing, participation in daily activities, and rehabilitation engagement, potentially reducing unplanned care visits, GP appointments, and less dependence on expensive formal care. It may also improve participation in education and employment, offering broader social and economic benefits. Therefore, the committee was of a view that fatigue management is likely to represent a cost-effective use of NHS resources.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.14.3, 1.15.1 to 1.15.7 and the research recommendation on fatigue management.

References – included studies

Effectiveness

Carter 2014

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Hersche 2019

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Rytter 2019

Rytter, H.M., Westenbaek, K., Henriksen, H. et al. (2019) Specialized interdisciplinary rehabilitation reduces persistent post-concussive symptoms: a randomized clinical trial. Brain Injury 33(3): 266-281

Thomas 2017

Thomas, S, Fazakarley, L, Thomas, PW et al. (2017) Mii-vitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis. BMJ open 7(9): e016966

Veenhuizen 2019

Veenhuizen, Y., Cup, E.H.C., Jonker, M.A. et al. (2019) Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial. Neurology 93(18): e1720-e1731

Economic

No economic studies were identified

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42024505254
1.	Review title	Rehabilitation for fatigue management
2.	Review question	What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?
3.	Objective	To determine the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management, for people with chronic neurological disorders.
4.	Searches	The following databases will be searched: • Medline All • Embase • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • PsycInfo • Social Policy and Practice Searches will be restricted by: • Date: 2013 onwards • English language • Human studies • Systematic Reviews

ID	Field	Content
		• RCTs • Non-randomised studies Other searches: • Inclusion lists of systematic reviews With the agreement of the guideline committee the searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management for people with chronic neurological disorders
6.	Population	Inclusion: Adults and children with rehabilitation needs due to the following chronic neurological disorders: • Acquired brain injury • Acquired spinal cord injury • Acquired peripheral nerve disorders • Progressive neurological diseases • Functional neurological disorders Exclusion: • Conditions which do not fit one of the 5 categories of chronic neurological disorder as defined in the guideline scope. These exclusions will be by exception and examined on a case-by-case basis rather than whole disorder groups. For example, this guideline will not cover autonomic neuropathy or the acute stabilisation of conditions such as encephalitis or hydrocephalus and will not cover degenerative disc disorder as spinal discs do not form part of the spinal cord. • Disorders for which interventions are primarily focused on altering body structure and functions, for example isolated peripheral nerve injuries such as single nerve or plexus injuries.

ID	Field	Content
		• Surgical management of conditions (for example brain tumours, orthopaedic complications). • Conditions for which NICE rehabilitation and rehabilitation related recommendations already exist, including stroke in people aged 16 years and over, dementia including Alzheimer's disease, cerebral palsy, myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome and post-COVID-19 syndrome. • Early rehabilitation after spinal cord injury as this will be covered in the NICE guideline on rehabilitation after traumatic injury
7.	Intervention	Inclusion: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management. Exclusion: • Unimodal, single component interventions for fatigue management • Pharmacological treatment for fatigue management

8.	Comparator	Interventions compared with others in the same group or:
		• Uni-modal rehabilitation for fatigue management (physical or psychological interventions)
		• Placebo (placebo or sham)
		• Control (no intervention, waitlist, standard rehabilitation care alone, or 'usual care')
		• The same intervention (as listed under 'intervention') but varied in terms of:
		  ○ Frequency
		  ○ Intensity
		  ○ Timing
		  ○ Setting

9.	Types of study to be included	Include published full-text papers**: • Systematic reviews of RCTs • Experimental studies with random assignment to intervention and control groups. If insufficient* RCT evidence is located to support decision making about children and young people, then experimental studies with non-random assignment to intervention and control groups (quasi-randomised controlled trials, non-randomised controlled trials and prospective and

ID	Field	Content
		retrospective cohort studies) will also be considered, if a method of controlling for confounding variables is used. Systematic reviews of these studies will also be considered. *Sufficiency will be judged on issues such as the number and quality of the included studies; sample sizes, reported outcomes, and availability of data on subgroups of interest. **Studies must match or adjust for age and chronic neurological disorder. Other confounding factors are: • Sex • delivery setting, for instance whether community or inpatient.
10.	Other exclusion criteria	Inclusion: • Full text papers • Studies conducted in the UK, Australia, New Zealand and Canada and high-income European countries (according to the World Bank). Exclusion: • Conference abstracts/proceedings • Non-English language articles • Articles published before 2013 • Books, book chapters and theses. • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality.
11.	Context	Recommendations will apply to all inpatient (excluding critical care units), outpatient and community settings, including tertiary settings and care homes in which either fully or partially NHS-funded rehabilitation interventions for chronic neurological disorders are provided.
12.	Primary outcomes (critical outcomes)	• **Fatigue severity or impact on fatigue** (assessed using a validated, global, patient-reported measure of fatigue such as the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Fatigue Impact Scale (FIS), the Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F) and the PEDS-QL MFS)

ID	Field	Content
13.	Secondary outcomes (important outcomes)	Not applicable.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records (or 300 records, whichever is smaller); 90% agreement is required and disagreements will be resolved via discussion with the senior systematic reviewer. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. The included and excluded studies lists will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair. A standardised form will be used to extract the following data from included studies: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. This will be quality assessed by the senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane ROBINS-I tool for non-randomised controlled trials.

ID	Field	Content
		• The quality assessment will be performed by one reviewer and this will be quality assessed by the senior reviewer.

16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.
		
		The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.grade-workinggroup.org/
		
		Importance and imprecision of findings will be assessed against minimally important differences (MIDs). Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes
		• For risk ratios: 0.8 and 1.25.
		• For continuous outcomes:
		  ○ MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD.
		  ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.

17.	Analysis of sub-groups	Evidence will be stratified by: • Age at time of intervention (children vs. adults). Children are classified as being aged 17 years or younger.

ID	Field	Content	
		• Functional neurological disorders as distinct from the 4 other categories of neurological disorder. • Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • The 4 disorder categories not separated out through a priori stratification (acquired brain injury, acquired spinal cord injury, acquired peripheral nerve disorders and progressive neurological diseases) • Study design (RCT v. NRS) • Age (for the ≤17 years of age stratification only). Categories are <4 years, 4-11 years and >11 years Where evidence is stratified or sub-grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	January 2024	

ID	Field	Content		
22.	Anticipated completion date	July 2024		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a Named contact National Institute for Health and Care Excellence (NICE) 5b Named contact e-mail rehabforcnd@nice.org.uk 5c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	NICE review team		
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

ID	Field	Content	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10181.	
29.	Other registration details	Not applicable	
30.	Reference/URL for published protocol	crd.york.ac.uk/PROSPERO/display_record.php?RecordID=505254	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE web-site, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Quantitative; effectiveness; personal care, activities of daily living, rehabilitation	
33.	Details of existing review of same topic by same authors	Not applicable.	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☒	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	Not applicable	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane database of systematic reviews; CENTRAL: Cochrane central register of controlled trials; GRADE: grading of recommendations assessment, development and evaluation; INAHTA: international network of agencies for health technology assessment; MEDLINE: medical literature analysis and retrieval system online; MID: minimally important difference; NRS: non-randomised trials; PEDS-QL MFS: pediatric quality of life Inventory multidimensional fatigue scale; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias In non-randomised studies - of Interventions; ROBIS: risk of bias in systematic reviews; SMD: standard mean difference; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Review question search strategies

Databases: Medline all

Date of last search: 29/01/2024

#	Searches
1	(CRANIOCEREBRAL TRAUMA/ or brain injuries/ or exp brain hemorrhage, traumatic/ or exp brain injuries, diffuse/ or exp brain injuries, traumatic/ or exp brain injury, chronic/ or Shaken Baby Syndrome/ or HYPOXIA, BRAIN/ or Brain Damage, Chronic/ or exp INTRACRANIAL HEMORRHAGE, TRAUMATIC/ or exp BRAIN NEOPLASMS/ or BRAIN DISEASES/ or BRAIN ABSCESS/ or BRAIN DISEASES, METABOLIC/ or CEREBELLAR DISEASES/ or cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or cerebrovascular trauma/ or intracranial arteriovenous malformations/ or "intracranial embolism and thrombosis"/ or intracranial hemorrhages/ or vascular headaches/ or exp ENCEPHALITIS/ or exp HYDROCEPHALUS/) not (exp STROKE/ or dementia/)
2	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) adj2 (injur* or trauma* or damage* or disease*1 or disorder* or infect* or h?emorrhag* or neoplasm* or cancer* or tumo?r* or insult* or impair* or ischemi* or ischaemi* or infarcti* or hypoxi* or drown*)).ti,ab.
3	(chronic* adj1 trauma* adj2 encephalopath*).ti,ab.
4	((infratentorial* or supratentorial* or hypothalam* or pituitar* or choroid plexus) adj2 (neoplasm* or cancer* or tumo?r* or carcinom* or adenocarcinom*)).ti,ab.
5	(brain* adj2 abscess*).ti,ab.
6	(carotid arter* adj2 (disease* or injur*)).ti,ab.
7	("basal ganglia disease*" or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cereb* degenerat*" or "shak* baby syndrome*").ti,ab.
8	exp STROKE/ and (ADOLESCENT/ or MINORS/ or exp CHILD/ or exp INFANT/ or exp PEDIATRICS/ or exp PUBERTY/)
9	(stroke? adj3 (p?ediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or under-age* or "under age*" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school age*" or schoolage* or "under 16" or "under sixteen*")).ti,ab.
10	exp SPINAL CORD INJURIES/ or exp SPINAL CORD NEOPLASMS/ or EPIDURAL ABSCESS/ or SPINAL CORD DISEASES/ or exp SPINAL CORD VASCULAR DISEASES/ or SPINAL CORD COMPRESSION/ or MYELITIS, TRANSVERSE/
11	((spinal* or spine?) adj2 (injur* or trauma* or tumo?r* or neoplasm* or cancer* or infect* or insult* or disease? or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or h?emorrhag*)).ti,ab.
12	(Central cord syndrome* or transverse myelitis).ti,ab.
13	(epidural* adj2 (neoplasm* or cancer* or tumo?r* or abscess*)).ti,ab.
14	((spinal* or spine?) adj2 (viral* or virus* or polio* or acquired immunodeficiency syndrome or AIDS or HIV or bacterial* or neurosyphili* or neuro-syphili* or tubercul*)).ti,ab.
15	PERIPHERAL NERVE INJURIES/ or exp CRANIAL NERVE INJURIES/ or PERIPHERAL NERVOUS SYSTEM NEOPLASMS/ or exp CRANIAL NERVE NEOPLASMS/ or exp PERIPHERAL NERVOUS SYSTEM DISEASES/ or exp CRANIAL NERVE DISEASES/
16	((periph* or cranial*) adj1 (nerve? or nervous system) adj2 (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumo?r* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome?)).ti,ab.
17	(Guillain* adj1 Barr*).ti,ab.
18	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 injur*).ti,ab.
19	(optic* adj1 nerve* adj2 (neoplasm* or cancer* or tumo?r*)).ti,ab.
20	(brachial plexus adj1 (neuropath* or neuritis)).ti,ab.
21	(complex regional pain syndrome* or causalgia or mononeuropath* or nerve compression syndrome*).ti,ab.
22	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) adj1 neuropath*).ti,ab.
23	((carpal-tunnel or piriformis-muscle or tarsal-tunnel or thoracic-outlet) adj1 syndrome*).ti,ab.

#	Searches
24	(pudendal neuralgia or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*).ti,ab.
25	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 disease*).ti,ab.
26	(periph* adj2 neuropath*).ti,ab.
27	(((periph* or cranial*) adj2 (nerve? or nervous system)) and lupus).ti,ab.
28	((multi-focal* or multifocal*) adj2 motor adj1 neuropath*).ti,ab.
29	(((periph* or cranial*) adj2 (nerve? or nervous system)) and alcohol*).ti,ab.
30	exp MOTOR NEURON DISEASE/ or POSTPOLIOMYELITIS SYNDROME/ or exp PARKINSONIAN DISORDERS/ or MUSCULAR DYSTROPHY, DUCHENNE/ or exp MULTIPLE SCLEROSIS/ or NEUROMUSCULAR DISEASES/ or SPASTIC PARAPLEGIA, HEREDITARY/ or FRIEDREICH ATAXIA/ or exp MULTIPLE SYSTEM ATROPHY/ or SUPRANUCLEAR PALSY, PROGRESSIVE/ or CORTICOBASAL DEGENERATION/ or LEUKODYSTROPHY, METACHROMATIC/ or exp MITOCHONDRIAL MYOPATHIES/ or exp MUCOPOLYSACCHARIDOSES/ or WILLIAMS SYNDROME/ or GENETIC DISEASES, INBORN/ or RETT SYNDROME/ or FETAL ALCOHOL SPECTRUM DISORDERS/ or DYSTONIC DISORDERS/ or "HEREDITARY SENSORY AND MOTOR NEUROPATHY"/ or SPINAL DYSRAPHISM/
31	(neurolog* adj1 (condition* or disease* or damage* or disorder* or impair*)).ti,ab.
32	((motor-neuron* or gehrig* or charcott* or kennedy*) adj1 disease*).ti,ab.
33	((amyotroph* or primary) adj1 lateral* adj1 sclero*).ti,ab.
34	(bulbar adj1 pals*).ti,ab.
35	((muscular or muscle* or bulbo) adj1 atroph* adj1 spin*).ti,ab.
36	(progressiv* adj1 (muscular or muscle*) adj1 atroph*).ti,ab.
37	((postpolio* or post-polio*) adj1 syndrome?).ti,ab.
38	(Parkinson* or duchenne* or multiple scleros?s* or aphasia or creutzfeldt-jakob or huntington* or kluver-bucy).ti,ab.
39	(muscular adj1 dystroph*).ti,ab.
40	(neuromusc* adj1 (disease* or disorder?)).ti,ab.
41	(heredit* adj1 spastic* adj1 parapleg*).ti,ab.
42	"friedreich* ataxia*".ti,ab.
43	((multiple system or olivopontocerebellar) adj1 atroph*).ti,ab.
44	(shy-drager syndrome* or striatonigral degenerat* or batten* disease?).ti,ab.
45	(progressive adj1 supranuclear adj1 pals*).ti,ab.
46	(richardson* adj1 (disease? or syndrome?)).ti,ab.
47	((corticobasal or cortico basal) adj1 degenerat*).ti,ab.
48	(white adj1 matter adj1 disorder?).ti,ab.
49	(metachromatic leukodystroph* or mitochondrial myopath* or mucopolysaccharidos*).ti,ab.
50	(lysosomal adj1 storage adj1 disorder?).ti,ab.
51	((genetic or William* or catch-22 or rett* or congenital or f?etal alcohol) adj1 (syndrome or disorder*)).ti,ab.
52	(perinatal illness* or perinatal hypoxia*).ti,ab.
53	(primary adj1 dystonia?).ti,ab.
54	(heredit* adj1 motor* adj1 sens* adj1 neuropath*).ti,ab.
55	(spina bifida? or spinal dysraphism?).ti,ab.
56	MOVEMENT DISORDERS/ or MOTOR DISORDERS/ or CONVERSION DISORDER/
57	((functional* or psychogenic* or dissociative*) adj1 neurologic* adj1 (disorder* or dysfunction* or difficult*)).ti,ab.
58	((movement* or motor* or convers*) adj1 (disorder* or dysfunct*)).ti,ab.
59	((psychogenic or dissociative or non-epilep* or nonepilep*) adj1 (seizure* or convulsion* or fit or fits or spasm* or attack*)).ti,ab.
60	(pseudo-seizure* or pseudoseizure*).ti,ab.
61	(medical* adj1 (unexplain* or un-explain*) adj1 symptom?).ti,ab.
62	or/1-61
63	FATIGUE/
64	MENTAL FATIGUE/
65	MUSCLE FATIGUE/

#	Searches
66	fatig*.ti.
67	fatig*.ab. /freq=2
68	(lassitude or brain fog* or tired* or exhaustion or exhausted or abulia or akinesia).ti,ab.
69	(cloud* adj3 conscious*).ti,ab.
70	LETHARGY/
71	letharg*.ti,ab.
72	APATHY/
73	apath*.ti,ab.
74	ASTHENIA/
75	asthenia.ti,ab.
76	NEURASTHENIA/
77	neurasthenia.ti,ab.
78	or/63-77
79	62 and 78
80	letter/
81	editorial/
82	news/
83	exp historical article/
84	Anecdotes as topic/
85	comment/
86	case reports/
87	(letter or comment*).ti.
88	or/80-87
89	randomized controlled trial/ or random*.ti,ab.
90	88 not 89
91	animals/ not humans/
92	exp Animals, Laboratory/
93	exp Animal Experimentation/
94	exp Models, Animal/
95	exp Rodentia/
96	(rat or rats or rodent* or mouse or mice).ti.
97	or/90-96
98	79 not 97
99	limit 98 to english language
100	limit 99 to yr="2013 -Current"
101	meta-analysis/
102	meta-analysis as topic/
103	(meta analy* or metanaly* or metaanaly*).ti,ab.
104	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
105	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
106	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
107	(search* adj4 literature).ab.
108	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
109	cochrane.jw.
110	or/101-109
111	randomized controlled trial.pt.
112	controlled clinical trial.pt.
113	pragmatic clinical trial.pt.
114	randomi#ed.ab.
115	placebo.ab.
116	randomly.ab.
117	Clinical Trials as topic.sh.

#	Searches
118	trial.ti.
119	or/111-118
120	exp EPIDEMIOLOGIC STUDIES/ or exp CLINICAL TRIAL/ or COMPARATIVE STUDY/
121	(control and study).mp.
122	program.mp.
123	or/120-122
124	exp Infant/ or Infant Health/ or Infant Welfare/
125	(prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
126	exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/
127	Minors/
128	(child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn.
129	exp pediatrics/
130	(pediatric* or paediatric* or peadiatric*).ti,ab,in,jn.
131	Adolescent/ or Adolescent Behavior/ or Adolescent Health/
132	Puberty/
133	(adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
134	Schools/
135	Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/
136	(pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn.
137	("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab.
138	or/124-137
139	100 and (110 or 119)
140	100 and 123 and 138
141	or/139-140

Databases: Embase

Date of last search: 29/01/2024

#	Searches
1	(head injury/ or exp brain injury/ or chronic brain disease/ or brain hemorrhage/ or brain hypoxia/ or exp brain tumor/ or brain disease/ or brain abscess/ or metabolic encephalopathy/ or cerebellum disease/ or exp cerebrovascular disease/ or encephalitis/ or hydrocephalus/) not (exp cerebrovascular accident/ or dementia/)
2	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) adj2 (injur* or trauma* or damage* or disease*1 or disorder* or infect* or h?emorrhag* or neoplasm* or cancer* or tumo?r* or insult* or impair* or ischemi* or infarcti* or hypoxi* or drown*)).ti,ab.
3	(chronic* adj1 trauma* adj2 encephalopath*).ti,ab.
4	((infratentorial* or supratentorial* or hypothalam* or pituitar* or choroid plexus) adj2 (neoplasm* or cancer* or tumo?r* or carcinom* or adenocarcinom*)).ti,ab.
5	(brain* adj2 abscess*).ti,ab.
6	(carotid arter* adj2 (disease* or injur*)).ti,ab.
7	("basal ganglia disease*" or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cereb* degenerat*" or "shak* baby syndrome*").ti,ab.
8	exp cerebrovascular accident/ and (adolescent/ or "minor (person)"/ or exp child/ or exp infant/ or pediatrics/ or exp pediatrics/ or exp puberty/)
9	(stroke? adj3 (p?ediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or under-age* or "under age*" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school age*" or schoolage* or "under 16" or "under sixteen*")).ti,ab.
10	exp spinal cord injury/ or exp spinal cord tumor/ or epidural abscess/ or spinal cord disease/ or exp spinal cord vascular disease/ or spinal cord compression/ or transverse myelitis/

#	Searches
11	((spinal* or spine?) adj2 (injur* or trauma* or tumo?r* or neoplasm* or cancer* or infect* or insult* or disease? or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or h?emorrhag*)).ti,ab.
12	(Central cord syndrome* or transverse myelitis).ti,ab.
13	(epidural* adj2 (neoplasm* or cancer* or tumo?r* or abscess*)).ti,ab.
14	((spinal* or spine?) adj2 (viral* or virus* or polio* or acquired immunodeficiency syndrome or AIDS or HIV or bacterial* or neurosyphili* or neuro-syphili* or tubercul*)).ti,ab.
15	peripheral nerve injury/ or exp cranial nerve injury/ or peripheral nerve tumor/ or exp cranial nerve tumor/ or exp peripheral neuropathy/ or exp cranial neuropathy/
16	((periph* or cranial*) adj1 (nerve? or nervous system) adj2 (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumo?r* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome?)).ti,ab.
17	(Guillain* adj1 Barr*).ti,ab.
18	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 injur*).ti,ab.
19	(optic* adj1 nerve* adj2 (neoplasm* or cancer* or tumo?r*)).ti,ab.
20	(brachial plexus adj1 (neuropath* or neuritis)).ti,ab.
21	(complex regional pain syndrome* or causalgia or mononeuropath* or nerve compression syndrome*).ti,ab.
22	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) adj1 neuropath*).ti,ab.
23	((carpal-tunnel or piriformis-muscle or tarsal-tunnel or thoracic-outlet) adj1 syndrome*).ti,ab.
24	(pudendal neuralgia or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*).ti,ab.
25	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 disease*).ti,ab.
26	(periph* adj2 neuropath*).ti,ab.
27	(((periph* or cranial*) adj2 (nerve? or nervous system)) and lupus).ti,ab.
28	((multi-focal* or multifocal*) adj2 motor adj1 neuropath*).ti,ab.
29	(((periph* or cranial*) adj2 (nerve? or nervous system)) and alcohol*).ti,ab.
30	exp motor neuron disease/ or postpoliomyelitis syndrome/ or exp parkinsonism/ or Duchenne muscular dystrophy/ or exp multiple sclerosis/ or neuromuscular disease/ or hereditary motor sensory neuropathy/ or Friedreich ataxia/ or exp Shy Drager syndrome/ or progressive supranuclear palsy/ or corticobasal degeneration/ or metachromatic leukodystrophy/ or exp mitochondrial myopathy/ or exp mucopolysaccharidosis/ or Williams Beuren syndrome/ or genetic disorder/ or Rett syndrome/ or fetal alcohol syndrome/ or dystonic disorder/ or hereditary motor sensory neuropathy/ or spinal dysraphism/
31	(neurolog* adj1 (condition* or disease* or damage* or disorder* or impair*)).ti,ab.
32	((motor-neuron* or gehrig* or charcott* or kennedy*) adj1 disease*).ti,ab.
33	((amyotroph* or primary) adj1 lateral* adj1 sclero*).ti,ab.
34	(bulbar adj1 pals*).ti,ab.
35	((muscular or muscle* or bulbo) adj1 atroph* adj1 spin*).ti,ab.
36	(progressiv* adj1 (muscular or muscle*) adj1 atroph*).ti,ab.
37	((postpolio* or post-polio*) adj1 syndrome?).ti,ab.
38	(Parkinson* or duchenne* or multiple scleros?s* or aphasia or creutzfeldt-jakob or huntington* or kluver-bucy).ti,ab.
39	(muscular adj1 dystroph*).ti,ab.
40	(neuromusc* adj1 (disease* or disorder?)).ti,ab.
41	(heredit* adj1 spastic* adj1 parapleg*).ti,ab.
42	"friedreich* ataxia*".ti,ab.
43	((multiple system or olivopontocerebellar) adj1 atroph*).ti,ab.
44	(shy-drager syndrome* or striatonigral degenerat* or batten* disease?).ti,ab.
45	(progressive adj1 supranuclear adj1 pals*).ti,ab.
46	(richardson* adj1 (disease? or syndrome?)).ti,ab.
47	((corticobasal or cortico basal) adj1 degenerat*).ti,ab.
48	(white adj1 matter adj1 disorder?).ti,ab.
49	(metachromatic leukodystroph* or mitochondrial myopath* or mucopolysaccharidos*).ti,ab.
50	(lysosomal adj1 storage adj1 disorder?).ti,ab.

#	Searches
51	((genetic or William* or catch-22 or rett* or congenital or f?etal alcohol) adj1 (syndrome or disorder*)).ti,ab.
52	(perinatal illness* or perinatal hypoxia*).ti,ab.
53	(primary adj1 dystonia?).ti,ab.
54	(heredit* adj1 motor* adj1 sens* adj1 neuropath*).ti,ab.
55	(spina bifida? or spinal dysraphism?).ti,ab.
56	motor dysfunction/ or motor dysfunction/ or conversion disorder/
57	((functional* or psychogenic* or dissociative*) adj1 neurologic* adj1 (disorder* or dysfunction* or difficult*)).ti,ab.
58	((movement* or motor* or convers*) adj1 (disorder* or dysfunct*)).ti,ab.
59	((psychogenic or dissociative or non-epilep* or nonepilep*) adj1 (seizure* or convulsion* or fit or fits or spasm* or attack*)).ti,ab.
60	(pseudo-seizure* or pseudoseizure*).ti,ab.
61	(medical* adj1 (unexplain* or un-explain*) adj1 symptom?).ti,ab.
62	or/1-61
63	*FATIGUE/
64	MENTAL FATIGUE/
65	MUSCLE FATIGUE/
66	LASSITUDE/
67	CLOUDING OF CONSCIOUSNESS/
68	EXHAUSTION/
69	AKINESIA/
70	fatig*.ti.
71	fatig*.ab. /freq=2
72	(lassitude or brain fog* or tired* or exhaustion or exhausted or abulia or akinesia).ti,ab.
73	(cloud* adj3 conscious*).ti,ab.
74	*LETHARGY/
75	letharg*.ti,ab.
76	*APATHY/
77	apath*.ti,ab.
78	*ASTHENIA/
79	asthenia.ti,ab.
80	NEURASTHENIA/
81	neurasthenia.ti,ab.
82	or/63-81
83	62 and 82
84	letter.pt. or letter/
85	note.pt.
86	editorial.pt.
87	case report/ or case study/
88	(letter or comment*).ti.
89	or/84-88
90	randomized controlled trial/ or random*.ti,ab.
91	89 not 90
92	animal/ not human/
93	nonhuman/
94	exp Animal Experiment/
95	exp Experimental Animal/
96	animal model/
97	exp Rodent/
98	(rat or rats or rodent* or mouse or mice).ti.
99	or/91-98
100	83 not 99

#	Searches
101	limit 100 to english language
102	limit 101 to yr="2013 -Current"
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
108	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
109	(search* adj4 literature).ab.
110	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
111	((pool* or combined) adj2 (data or trials or studies or results)).ab.
112	cochrane.jw.
113	or/103-112
114	random*.ti,ab.
115	factorial*.ti,ab.
116	(crossover* or cross over*).ti,ab.
117	((doubl* or singl*) adj blind*).ti,ab.
118	(assign* or allocat* or volunteer* or placebo*).ti,ab.
119	crossover procedure/
120	single blind procedure/
121	randomized controlled trial/
122	double blind procedure/
123	or/114-122
124	EPIDEMIOLOGY/ or CONTROLLED STUDY/ or exp CASE CONTROL STUDY/ or PROSPECTIVE STUDY/ or RETROSPECTIVE STUDY/ or COHORT ANALYSIS/ or FOLLOW UP/ or CROSS-SECTIONAL STUDY/ or exp CLINICAL TRIAL/ or COMPARATIVE STUDY/
125	(control and study).mp.
126	program.mp.
127	or/124-126
128	exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/
129	(prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw.
130	(child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw.
131	exp pediatrics/
132	(pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw.
133	exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/
134	(adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw.
135	school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/
136	(pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw.
137	("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab.
138	or/128-137
139	102 and (113 or 123)
140	102 and 127 and 138
141	or/139-140
142	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
143	141 not 142

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

Date of last search: 29/01/2024

#	Searches
#1	MeSH descriptor: [Craniocerebral Trauma] this term only
#2	MeSH descriptor: [Brain Injuries] this term only
#3	MeSH descriptor: [Brain Hemorrhage, Traumatic] explode all trees
#4	MeSH descriptor: [Brain Injuries, Diffuse] explode all trees
#5	MeSH descriptor: [Brain Injuries, Traumatic] explode all trees
#6	MeSH descriptor: [Brain Injury, Chronic] explode all trees
#7	MeSH descriptor: [Shaken Baby Syndrome] this term only
#8	MeSH descriptor: [Brain Damage, Chronic] this term only
#9	MeSH descriptor: [Hypoxia, Brain] this term only
#10	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#11	MeSH descriptor: [Brain Neoplasms] explode all trees
#12	MeSH descriptor: [Brain Diseases] this term only
#13	MeSH descriptor: [Brain Abscess] this term only
#14	MeSH descriptor: [Brain Diseases, Metabolic] this term only
#15	MeSH descriptor: [Cerebellar Diseases] this term only
#16	MeSH descriptor: [Cerebrovascular Disorders] this term only
#17	MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] this term only
#18	MeSH descriptor: [Cerebrovascular Trauma] this term only
#19	MeSH descriptor: [Intracranial Arteriovenous Malformations] this term only
#20	MeSH descriptor: [Intracranial Embolism and Thrombosis] this term only
#21	MeSH descriptor: [Intracranial Hemorrhages] this term only
#22	MeSH descriptor: [Vascular Headaches] this term only
#23	MeSH descriptor: [Encephalitis] this term only
#24	MeSH descriptor: [Hydrocephalus] this term only
#25	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	MeSH descriptor: [Stroke] explode all trees
#27	MeSH descriptor: [Dementia] this term only
#28	#26 or #27
#29	#25 NOT #28
#30	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) NEAR/2 (injur* or trauma* or damage* or disease* or diseases* or disorder* or infect* or hemorrhag* or haemorrhag* or neoplasm* or cancer* or tumour* or tumor* or insult* or impair* or ischemi* or ischaemi* or infarcti* or hypoxi* or drown*)):ti,ab
#31	(chronic* NEAR/1 trauma* NEAR/2 encephalopath*):ti,ab
#32	((infratentorial* or supratentorial* or hypothalam* or pituitar* or "choroid plexus") NEAR/2 (neoplasm* or cancer* or tumour* or tumor* or carcinom* or adenocarcinom*)):ti,ab
#33	(brain* NEAR/2 abscess*):ti,ab
#34	(carotid arter* NEAR/2 (disease* or injur*)):ti,ab
#35	(("basal ganglia" next disease*) or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cerebellar" next degenerat* or "shaken baby" next syndrome* or "shaking baby" next syndrome*):ti,ab
#36	MeSH descriptor: [Stroke] explode all trees
#37	MeSH descriptor: [Adolescent] this term only
#38	MeSH descriptor: [Minors] this term only
#39	MeSH descriptor: [Child] explode all trees
#40	MeSH descriptor: [Infant] explode all trees
#41	MeSH descriptor: [Pediatrics] explode all trees
#42	MeSH descriptor: [Puberty] explode all trees
#43	#37 or #38 or #39 or #40 or #41 or #42
#44	#36 and #43

#	Searches
#45	((stroke or strokes) NEAR/3 (paediatric* or pediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or "under age" or "under ages" or "under aged" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school ages" or "school age" or "school aged" or schoolage* or "under 16" or "under sixteen" or "under sixteens")):ti,ab
#46	MeSH descriptor: [Spinal Cord Injuries] explode all trees
#47	MeSH descriptor: [Spinal Cord Neoplasms] explode all trees
#48	MeSH descriptor: [Epidural Abscess] this term only
#49	MeSH descriptor: [Spinal Cord Diseases] this term only
#50	MeSH descriptor: [Spinal Cord Vascular Diseases] explode all trees
#51	MeSH descriptor: [Spinal Cord Compression] this term only
#52	MeSH descriptor: [Myelitis, Transverse] this term only
#53	((spinal* or spine or spines) NEAR/2 (injur* or trauma* or tumour* or tumor* or neoplasm* or cancer* or infect* or insult* or disease or diseases or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or hemorrhag* or haemorrhag*)):ti,ab
#54	("Central cord" next syndrome* or "transverse myelitis"):ti,ab
#55	(epidural* NEAR/2 (neoplasm* or cancer* or tumour* or tumor* or abscess*)):ti,ab
#56	((spinal* or spine or spines) NEAR/2 (viral* or virus* or polio* or "acquired immunodeficiency syndrome" or AIDS or HIV or bacterial* or neurosyphili* or neuro next syphili* or tubercul*)):ti,ab
#57	MeSH descriptor: [Peripheral Nerve Injuries] this term only
#58	MeSH descriptor: [Cranial Nerve Injuries] explode all trees
#59	MeSH descriptor: [Peripheral Nervous System Neoplasms] this term only
#60	MeSH descriptor: [Cranial Nerve Neoplasms] explode all trees
#61	MeSH descriptor: [Peripheral Nervous System Diseases] explode all trees
#62	MeSH descriptor: [Cranial Nerve Diseases] explode all trees
#63	((periph* or cranial*) NEAR/1 (nerve or nerves or "nervous system") NEAR/2 (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumour* or tumor* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome*)):ti,ab
#64	(Guillain* NEAR/1 Barr*):ti,ab
#65	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or "ocular motility" or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) NEAR/1 nerve* NEAR/1 injur*):ti,ab
#66	(optic* NEAR/1 nerve* NEAR/2 (neoplasm* or cancer* or tumour* or tumor*)):ti,ab
#67	(brachial next plexus NEAR/1 (neuropath* or neuritis)):ti,ab
#68	("complex regional pain" next syndrome* or causalgia or mononeuropath* or "nerve compression" next syndrome*):ti,ab
#69	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) NEAR/1 neuropath*):ti,ab
#70	((carpal next tunnel or piriformis next muscle or tarsal next tunnel or thoracic next outlet) NEAR/1 syndrome*):ti,ab
#71	((pudendal next neuralgia) or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*):ti,ab
#72	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or "ocular motility" or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) NEAR/1 nerve* NEAR/1 disease*):ti,ab
#73	(periph* NEAR/2 neuropath*):ti,ab
#74	(((periph* or cranial*) NEAR/2 (nerve or nerves or "nervous system")) and lupus):ti,ab
#75	((multi next focal* or multifocal*) NEAR/2 motor NEAR/1 neuropath*):ti,ab
#76	(((periph* or cranial*) NEAR/2 (nerve or nerves or nervous system)) and alcohol*):ti,ab
#77	#29 or #30 or #31 or #32 or #33 or #34 or #35 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76
#78	MeSH descriptor: [Motor Neuron Disease] explode all trees
#79	MeSH descriptor: [Postpoliomyelitis Syndrome] this term only
#80	MeSH descriptor: [Parkinsonian Disorders] explode all trees
#81	MeSH descriptor: [Muscular Dystrophy, Duchenne] this term only
#82	MeSH descriptor: [Multiple Sclerosis] explode all trees
#83	MeSH descriptor: [Neuromuscular Diseases] this term only
#84	MeSH descriptor: [Spastic Paraplegia, Hereditary] this term only

#	Searches
#85	MeSH descriptor: [Friedreich Ataxia] this term only
#86	MeSH descriptor: [Multiple System Atrophy] explode all trees
#87	MeSH descriptor: [Supranuclear Palsy, Progressive] this term only
#88	MeSH descriptor: [Corticobasal Degeneration] explode all trees
#89	MeSH descriptor: [Leukodystrophy, Metachromatic] this term only
#90	MeSH descriptor: [Mitochondrial Myopathies] explode all trees
#91	MeSH descriptor: [Mucopolysaccharidoses] explode all trees
#92	MeSH descriptor: [Williams Syndrome] this term only
#93	MeSH descriptor: [Genetic Diseases, Inborn] this term only
#94	MeSH descriptor: [Rett Syndrome] this term only
#95	MeSH descriptor: [Fetal Alcohol Spectrum Disorders] this term only
#96	MeSH descriptor: [Dystonic Disorders] this term only
#97	MeSH descriptor: [Hereditary Sensory and Motor Neuropathy] this term only
#98	MeSH descriptor: [Spinal Dysraphism] this term only
#99	(neurolog* NEAR/1 (condition* or disease* or damage* or disorder* or impair*)):ti,ab
#100	((motor next neuron* or gehrig* or charcott* or kennedy*) NEAR/1 disease*):ti,ab
#101	((amyotroph* or primary) NEAR/1 lateral* NEAR/1 sclero*):ti,ab
#102	(bulbar NEAR/1 pals*):ti,ab
#103	((muscular or muscle* or bulbo) NEAR/1 atroph* NEAR/1 spin*):ti,ab
#104	(progressiv* NEAR/1 (muscular or muscle*) NEAR/1 atroph*):ti,ab
#105	((postpolio* or post next polio*) NEAR/1 (syndrome*)):ti,ab
#106	(Parkinson* or duchenne* or multiple next scleros* or sclerosos* or aphasia or creutzfeldt next jakob or huntington* or kluver next bucy):ti,ab
#107	(muscular NEAR/1 dystroph*):ti,ab
#108	((neurolog*) near/1 (condition* or disease* or damage* or disorder* or impair*)):ti,ab
#109	(heredit* NEAR/1 spastic* NEAR/1 parapleg*):ti,ab
#110	(friedreich* next ataxia*):ti,ab
#111	(("multiple system" or olivopontocerebellar) NEAR/1 atroph*):ti,ab
#112	((shy next drager next syndrome*) or striatonigral next degenerat* or batten next disease*):ti,ab
#113	(progressive NEAR/1 supranuclear NEAR/1 pals*):ti,ab
#114	(richardson* NEAR/1 (disease* or syndrome*)):ti,ab
#115	((corticobasal or "cortico basal") NEAR/1 degenerat*):ti,ab
#116	("white matter" NEAR/1 (disorder*)):ti,ab
#117	(metachromatic next leukodystroph* or mitochondrial next myopath* or mucopolysaccharidos*):ti,ab
#118	(lysosomal NEAR/1 storage NEAR/1 disorder*):ti,ab
#119	((genetic or William* or "catch-22" or rett* or congenital or fetal or "foetal alcohol") NEAR/1 (syndrome* or disorder*)):ti,ab
#120	(perinatal NEAR/1 (illness* or hypoxia*)):ti,ab
#121	(primary NEAR/1 (dystonia or dystonias)):ti,ab
#122	(heredit* NEAR/1 motor* NEAR/1 sens* NEAR/1 neuropath*):ti,ab
#123	(spina next (bifida or bifidas) or spinal next (dysraphism or dysraphisms)):ti,ab
#124	MeSH descriptor: [Movement Disorders] this term only
#125	MeSH descriptor: [Motor Disorders] this term only
#126	MeSH descriptor: [Conversion Disorder] this term only
#127	((functional* or psychogenic* or dissociative*) NEAR/1 neurologic* NEAR/1 (disorder* or dysfunction* or difficult*)):ti,ab
#128	((movement* or motor* or convers*) NEAR/1 (disorder* or dysfunct*)):ti,ab
#129	((psychogenic or dissociative or non-epilep* or nonepilep*) NEAR/1 (seizure* or convulsion* or fit or fits or spasm* or attack*)):ti,ab
#130	(pseudo next seizure or pseudoseizure):ti,ab
#131	(medical* NEAR/1 (unexplain* or un next explain*) NEAR/1 (symptom*)):ti,ab
#132	#77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or

#	Searches
	#117 or #118 or #119 or #120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131
#133	MeSH descriptor: [Fatigue] this term only
#134	MeSH descriptor: [Mental Fatigue] this term only
#135	MeSH descriptor: [Muscle Fatigue] this term only
#136	fatig*:ti,ab
#137	(lassitude or tired* or exhaustion or exhausted or abulia or akinesia):ti,ab
#138	(cloud* NEAR/3 conscious*):ti,ab
#139	(brain NEAR/1 fog*):ti,ab
#140	MeSH descriptor: [Lethargy] this term only
#141	letharg*:ti,ab
#142	MeSH descriptor: [Apathy] this term only
#143	apath*:ti,ab
#144	MeSH descriptor: [Neurocirculatory Asthenia] this term only
#145	asthenia:ti,ab
#146	MeSH descriptor: [Neurasthenia] this term only
#147	neurasthenia:ti,ab
#148	#133 or #134 or #135 or #136 or #137 or #138 or #139 or #140 or #141 or #142 or #143 or #144 or #145 or #146 or #147
#149	#132 and #148
#150	#132 and #148 with Cochrane Library publication date Between Jan 2013 and Jan 2024, in Cochrane Reviews
#151	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#152	#149 not #151
#153	"conference":pt
#154	#152 not #153
#155	#152 not #153 with Publication Year from 2013 to 2024, in Trials

Databases: PsycInfo

Date of last search: 29/01/2024

#	Searches
1	(exp Brain Injuries/ or anoxia/ or exp brain disorders/ or exp cerebrovascular disorders/ or exp headache/) not (exp Dementia/ or Cerebrovascular Accidents/)
2	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) adj2 (injur* or trauma* or damage* or disease*1 or disorder* or infect* or h?emorrhag* or neoplasm* or cancer* or tumo?r* or insult* or impair* or ischemi* or ischaemi* or infarcti* or hypoxi* or drown*)).ti,ab.
3	(chronic* adj1 trauma* adj2 encephalopath*).ti,ab.
4	((infratentorial* or supratentorial* or hypothalam* or pituitar* or choroid plexus) adj2 (neoplasm* or cancer* or tumo?r* or carcinom* or adenocarcinom*)).ti,ab.
5	(brain* adj2 abscess*).ti,ab.
6	(carotid arter* adj2 (disease* or injur*)).ti,ab.
7	("basal ganglia disease*" or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cereb* degenerat*" or "shak* baby syndrome*").ti,ab.
8	Cerebrovascular Accidents/ and (exp childhood development/ or exp adolescent development/ or pediatrics/ or puberty/)
9	(stroke? adj3 (p?ediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or under-age* or "under age*" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school age*" or schoolage* or "under 16" or "under sixteen*")).ti,ab.
10	spinal cord injuries/ or (Spinal Cord/ and neoplasms/) or (Cardiovascular Disorders/ and spinal cord/) or exp myelitis/

#	Searches
11	((spinal* or spine?) adj2 (injur* or trauma* or tumo?r* or neoplasm* or cancer* or infect* or insult* or disease? or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or h?emorrhag*)).ti,ab.
12	(Central cord syndrome* or transverse myelitis).ti,ab.
13	(epidural* adj2 (neoplasm* or cancer* or tumo?r* or abscess*)).ti,ab.
14	((spinal* or spine?) adj2 (viral* or virus* or polio* or acquired immunodeficiency syndrome or AIDS or HIV or bacterial* or neurosyphili* or neuro-syphili* or tubercul*)).ti,ab.
15	(exp Peripheral Nervous System/ and (Injuries/ or neoplasms/)) or nervous system disorders/
16	((periph* or cranial*) adj1 (nerve? or nervous system) adj2 (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumo?r* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome?)).ti,ab.
17	(Guillain* adj1 Barr*).ti,ab.
18	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 injur*).ti,ab.
19	(optic* adj1 nerve* adj2 (neoplasm* or cancer* or tumo?r*)).ti,ab.
20	(brachial plexus adj1 (neuropath* or neuritis)).ti,ab.
21	(complex regional pain syndrome* or causalgia or mononeuropath* or nerve compression syndrome*).ti,ab.
22	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) adj1 neuropath*).ti,ab.
23	((carpal-tunnel or piriformis-muscle or tarsal-tunnel or thoracic-outlet) adj1 syndrome*).ti,ab.
24	(pudendal neuralgia or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*).ti,ab.
25	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 disease*).ti,ab.
26	(periph* adj2 neuropath*).ti,ab.
27	(((periph* or cranial*) adj2 (nerve? or nervous system)) and lupus).ti,ab.
28	((multi-focal* or multifocal*) adj2 motor adj1 neuropath*).ti,ab.
29	(((periph* or cranial*) adj2 (nerve? or nervous system)) and alcohol*).ti,ab.
30	motor neurons/ or exp muscular disorders/ or exp neuromuscular disorders/ or multiple sclerosis/ or neurodegenerative diseases/ or Progressive Supranuclear Palsy/ or corticobasal degeneration/ or Metabolism Disorders/ or Williams Syndrome/ or genetic disorders/ or rett syndrome/ or fetal alcohol syndrome/ or exp peripheral neuropathy/ or spina bifida/
31	(neurolog* adj1 (condition* or disease* or damage* or disorder* or impair*)).ti,ab.
32	((motor-neuron* or gehrig* or charcott* or kennedy*) adj1 disease*).ti,ab.
33	((amyotroph* or primary) adj1 lateral* adj1 sclero*).ti,ab.
34	(bulbar adj1 pals*).ti,ab.
35	((muscular or muscle* or bulbo) adj1 atroph* adj1 spin*).ti,ab.
36	(progressiv* adj1 (muscular or muscle*) adj1 atroph*).ti,ab.
37	((postpolio* or post-polio*) adj1 syndrome?).ti,ab.
38	(Parkinson* or duchenne* or multiple scleros?s* or aphasia or creutzfeldt-jakob or huntington* or kluver-bucy).ti,ab.
39	(muscular adj1 dystroph*).ti,ab.
40	(neuromusc* adj1 (disease* or disorder?)).ti,ab.
41	(heredit* adj1 spastic* adj1 parapleg*).ti,ab.
42	"friedreich* ataxia*".ti,ab.
43	((multiple system or olivopontocerebellar) adj1 atroph*).ti,ab.
44	(shy-drager syndrome* or striatonigral degenerat* or batten* disease?).ti,ab.
45	(progressive adj1 supranuclear adj1 pals*).ti,ab.
46	(richardson* adj1 (disease? or syndrome?)).ti,ab.
47	((corticobasal or cortico basal) adj1 degenerat*).ti,ab.
48	(white adj1 matter adj1 disorder?).ti,ab.
49	(metachromatic leukodystroph* or mitochondrial myopath* or mucopolysaccharidos*).ti,ab.
50	(lysosomal adj1 storage adj1 disorder?).ti,ab.
51	((genetic or William* or catch-22 or rett* or congenital or f?etal alcohol) adj1 (syndrome or disorder*)).ti,ab.
52	(perinatal illness* or perinatal hypoxia*).ti,ab.

#	Searches
53	(primary adj1 dystonia?).ti,ab.
54	(heredit* adj1 motor* adj1 sens* adj1 neuropath*).ti,ab.
55	(spina bifida? or spinal dysraphism?).ti,ab.
56	conversion disorder/
57	((functional* or psychogenic* or dissociative*) adj1 neurologic* adj1 (disorder* or dysfunction* or diffi-cult*)).ti,ab.
58	((movement* or motor* or convers*) adj1 (disorder* or dysfunct*)).ti,ab.
59	((psychogenic or dissociative or non-epilep* or nonepilep*) adj1 (seizure* or convulsion* or fit or fits or spasm* or attack*)).ti,ab.
60	(pseudo-seizure* or pseudoseizure*).ti,ab.
61	(medical* adj1 (unexplain* or un-explain*) adj1 symptom?).ti,ab.
62	or/1-61
63	FATIGUE/
64	EMOTIONAL EXHAUSTION/
65	fatig*.ti.
66	fatig*.ab. /freq=2
67	(lassitude or brain fog* or tired* or exhaustion or exhausted or abulia or akinesia).ti,ab.
68	(cloud* adj3 conscious*).ti,ab.
69	letharg*.ti,ab.
70	APATHY/
71	apath*.ti,ab.
72	ASTHENIA/
73	asthenia.ti,ab.
74	NEURASTHENIA/
75	neurasthenia.ti,ab.
76	or/63-75
77	62 and 76
78	(letter or editorial or comment reply).dt. or case report/
79	(letter or comment*).ti.
80	or/78-79
81	exp randomized controlled trial/
82	random*.ti,ab.
83	or/81-82
84	80 not 83
85	animal.po.
86	(rat or rats or rodent* or mouse or mice).ti.
87	or/84-86
88	77 not 87
89	limit 88 to english language
90	limit 89 to yr="2013 -Current"
91	(meta analysis or "systematic review").md.
92	META ANALYSIS/
93	SYSTEMATIC REVIEW/
94	(meta analy* or metanaly* or metaanaly*).ti,ab.
95	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
96	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
97	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
98	(search* adj4 literature).ab.
99	((pool* or combined) adj2 (data or trials or studies or results)).ab.
100	(medline or pubmed or cochrane or embase or psychlit or psyclit or cinahl or science citation index or bids or cancerlit).ab.
101	or/91-100
102	clinical trial.md.

#	Searches
103	Clinical trials/
104	Randomized controlled trials/
105	Randomized clinical trials/
106	assign*.ti,ab.
107	allocat*.ti,ab.
108	crossover*.ti,ab.
109	cross over*.ti,ab.
110	((doubl* or singl*) adj blind*).ti,ab.
111	factorial*.ti,ab.
112	placebo*.ti,ab.
113	random*.ti,ab.
114	volunteer*.ti,ab.
115	trial?.ti,ab.
116	or/102-115
117	EPIDEMIOLOGY/ or PROSPECTIVE STUDIES/ or RETROSPECTIVE STUDIES/ or COHORT ANALYSIS/ or FOLLOWUP STUDIES/ or exp CLINICAL TRIALS/
118	(control and study).mp.
119	program.mp.
120	or/117-119
121	(adolescence 13 17 yrs or childhood birth 12 yrs or infancy 2 23 mo or neonatal birth 1 mo or preschool age 2 5 yrs or school age 6 12 yrs).ag.
122	Pediatrics/ or Puberty/ or Adolescence/
123	(child* or adolescen* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or prepubert* or pre pubert* or prepubescen* or pre pubescen* or preschool* or pre school* or preteen* or pre teen* or pubert* or pubescen* or schoolchild* or school age? or teen* or toddler* or young or youth?).ti,ab.
124	(child* or adolescen* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or prepubert* or pre pubert* or pubert* or schoolchild* or school age?).jw.
125	or/121-124
126	90 and (101 or 116)
127	90 and 120 and 125
128	or/126-127
129	limit 128 to ("0100 journal" or "0110 peer-reviewed journal")

Databases: Social policy and practice

Date of last search: 29/01/2024

#	Searches
1	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) adj2 (injur* or trauma* or damage* or disease*1 or disorder* or infect* or h?emorrhag* or neoplasm* or cancer* or tumo?r* or insult* or impair* or ischemi* or infarcti* or hypoxi* or drown*)).ti,ab.
2	((brain* or cereb* or craniocereb* or cranial or intracrani* or neurocognit*) and (injur* or trauma* or damage* or disease* or disorder* or infect* or h?emorrhag* or neoplasm* or cancer* or tumo?r* or insult* or impair* or ischemi* or infarcti* or hypoxi* or drown*)).hw.
3	(chronic* adj1 trauma* adj2 encephalopath*).ti,ab.
4	(chronic* and trauma* and encephalopath*).hw.
5	((infratentorial* or supratentorial* or hypothalam* or pituitar* or choroid plexus) adj2 (neoplasm* or cancer* or tumo?r* or carcinom* or adenocarcinom*)).ti,ab.
6	((infratentorial* or supratentorial* or hypothalam* or pituitar* or choroid plexus) and (neoplasm* or cancer* or tumo?r* or carcinom* or adenocarcinom*)).hw.
7	(brain* adj2 abscess*).ti,ab.
8	(brain* and abscess*).hw.
9	(carotid arter* adj2 (disease* or injur*)).ti,ab.
10	(carotid arter* and (disease* or injur*)).hw.

#	Searches
11	("basal ganglia disease*" or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cereb* degenerat*" or "shak* baby syndrome*").ti,ab.
12	("basal ganglia disease*" or encephalitis or meningoencephalitis or hydrocephal* or "paraneoplastic cereb* degenerat*" or "shak* baby syndrome*").hw.
13	(stroke? adj3 (p?ediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or under-age* or "under age*" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school age*" or schoolage* or "under 16" or "under sixteen*")).ti,ab.
14	(stroke? and (p?ediatric* or child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or underage* or under-age* or "under age*" or teen or teens or teenager* or juvenile* or boy or boys or boyhood or girl or girls or girlhood or schoolchild* or "school age*" or schoolage* or "under 16" or "under sixteen*")).hw.
15	((spinal* or spine?) adj2 (injur* or trauma* or tumo?r* or neoplasm* or cancer* or infect* or insult* or disease? or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or h?emorrhag*)).ti,ab.
16	((spinal* or spine?) and (injur* or trauma* or tumo?r* or neoplasm* or cancer* or infect* or insult* or disease? or disorder* or degenrat* or compress* or vascular* or ischemi* or ischaemi* or infarct* or h?emorrhag*)).hw.
17	(Central cord syndrome* or transverse myelitis).ti,ab.
18	(Central cord syndrome* or transverse myelitis).hw.
19	(epidural* adj2 (neoplasm* or cancer* or tumo?r* or abscess*)).ti,ab.
20	(epidural* and (neoplasm* or cancer* or tumo?r* or abscess*)).hw.
21	((spinal* or spine?) adj2 (viral* or virus* or polio* or acquired immunodeficiency syndrome or AIDS or HIV or bacterial* or neurosyphili* or neuro-syphili* or tubercul*)).ti,ab.
22	((spinal* or spine?) and (viral* or virus* or polio* or acquired immunodeficiency syndrome or bacterial* or neurosyphili* or neuro-syphili* or tubercul*)).hw.
23	((periph* or cranial*) adj1 (nerve? or nervous system) adj2 (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumo?r* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome?)).ti,ab.
24	((periph* or cranial*) and (nerve? or nervous system) and (injur* or trauma* or disorder* or disease* or damage* or neoplasm* or cancer* or tumo?r* or inflamm* or autoimmun* or paraneoplastic* or neuropath* or syndrome?)).hw.
25	(Guillain* adj1 Barr*).ti,ab.
26	(Guillain* and Barr*).hw.
27	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 injur*).ti,ab.
28	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) and nerve* and injur*).hw.
29	(optic* adj1 nerve* adj2 (neoplasm* or cancer* or tumo?r*)).ti,ab.
30	(optic* and nerve* and (neoplasm* or cancer* or tumo?r*)).hw.
31	(brachial plexus adj1 (neuropath* or neuritis)).ti,ab.
32	(brachial plexus and (neuropath* or neuritis)).hw.
33	(complex regional pain syndrome* or causalgia or mononeuropath* or nerve compression syndrome*).ti,ab.
34	(complex regional pain syndrome* or causalgia or mononeuropath* or nerve compression syndrome*).hw.
35	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) adj1 neuropath*).ti,ab.
36	((femoral or median or peroneal or radial or sciatic or tibial or ulnar) and neuropath*).hw.
37	((carpal-tunnel or piriformis-muscle or tarsal-tunnel or thoracic-outlet) adj1 syndrome*).ti,ab.
38	((carpal-tunnel or piriformis-muscle or tarsal-tunnel or thoracic-outlet) and syndrome*).hw.
39	(pudendal neuralgia or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*).ti,ab.
40	(pudendal neuralgia or polyneuropath* or polyradiculoneuropath* or polyradiculopath* or radiculopath*).hw.
41	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) adj1 nerve* adj1 disease*).ti,ab.
42	((abducen* or accessory or facial or glossopharyngeal or hypoglossal or oculomotor or ocular motility or olfactory or optic* or trigeminal or trochlear or vestibulocochlear) and nerve* and disease*).hw.
43	(periph* adj2 neuropath*).ti,ab.
44	(periph* and neuropath*).hw.

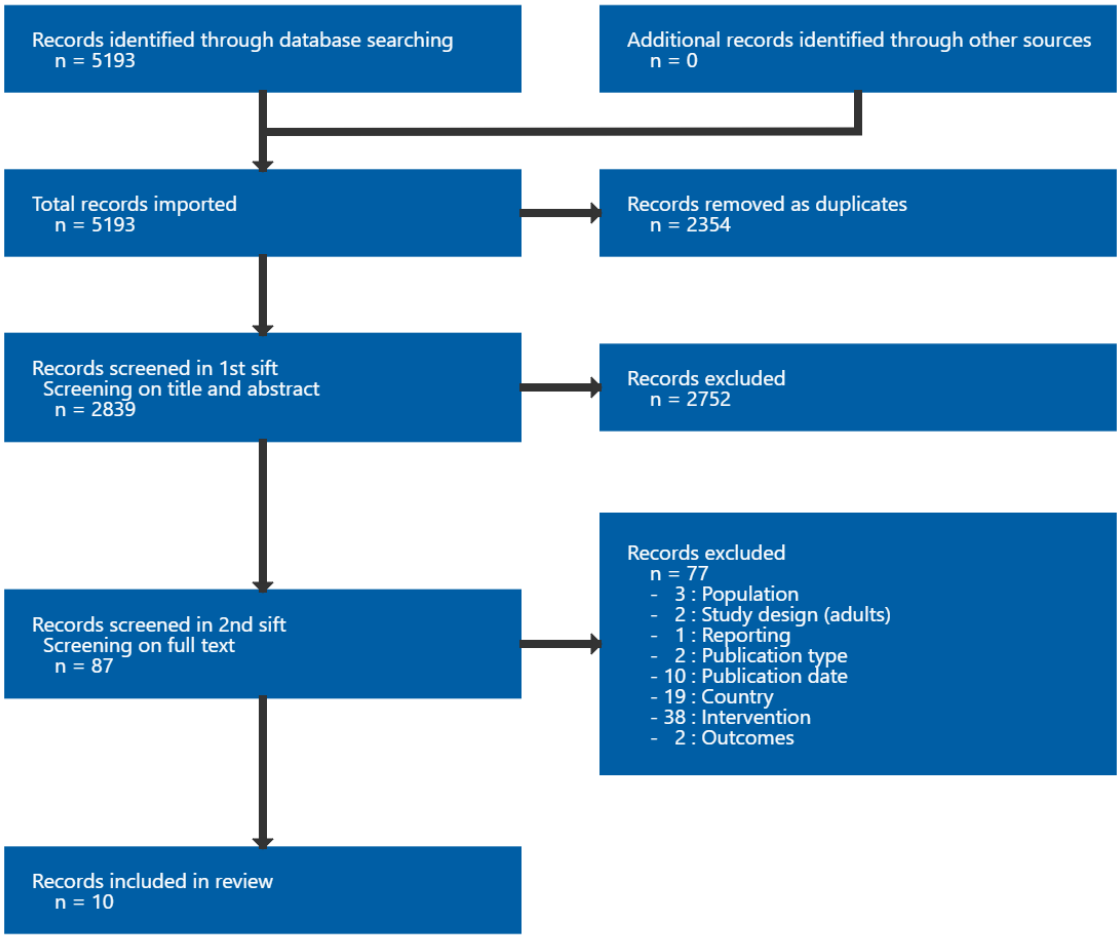
#	Searches
45	(((periph* or cranial*) adj2 (nerve? or nervous system)) and lupus).ti,ab.
46	((periph* or cranial*) and (nerve? or nervous system) and lupus).hw.
47	((multi-focal* or multifocal*) adj2 motor adj1 neuropath*).ti,ab.
48	((multi-focal* or multifocal*) and motor and neuropath*).hw.
49	(((periph* or cranial*) adj2 (nerve? or nervous system)) and alcohol*).ti,ab.
50	((periph* or cranial*) and (nerve? or nervous system) and alcohol*).hw.
51	(neurolog* adj1 (condition* or disease* or damage* or disorder* or impair*)).ti,ab.
52	(neurolog* and (condition* or disease* or damage* or disorder* or impair*)).hw.
53	((motor-neuron* or gehrig* or charcott* or kennedy*) adj1 disease*).ti,ab.
54	((motor-neuron* or gehrig* or charcott* or kennedy*) and disease*).hw.
55	((amyotroph* or primary) adj1 lateral* adj1 sclero*).ti,ab.
56	((amyotroph* or primary) and lateral* and sclero*).hw.
57	(bulbar adj1 pals*).ti,ab.
58	(bulbar and pals*).hw.
59	((muscular or muscle* or bulbo) adj1 atroph* adj1 spin*).ti,ab.
60	((muscular or muscle* or bulbo) and atroph* and spin*).hw.
61	(progressiv* adj1 (muscular or muscle*) adj1 atroph*).ti,ab.
62	(progressiv* and (muscular or muscle*) and atroph*).hw.
63	((postpolio* or post-polio*) adj1 syndrome?).ti,ab.
64	((postpolio* or post-polio*) and syndrome?).hw.
65	(Parkinson* or duchenne* or multiple scleros?s* or aphasia or creutzfeldt-jakob or huntington* or kluver-bucy).ti,ab.
66	(Parkinson* or duchenne* or multiple scleros?s* or aphasia or creutzfeldt-jakob or huntington* or kluver-bucy).hw.
67	(muscular adj1 dystroph*).ti,ab.
68	(muscular adj1 dystroph*).hw.
69	(neuromusc* adj1 (disease* or disorder?)).ti,ab.
70	(neuromusc* adj1 (disease* or disorder?)).hw.
71	(heredit* adj1 spastic* adj1 parapleg*).ti,ab.
72	(heredit* and spastic* and parapleg*).hw.
73	"friedreich* ataxia*".ti,ab.
74	"friedreich* ataxia*".hw.
75	((multiple system or olivopontocerebellar) adj1 atroph*).ti,ab.
76	((multiple system or olivopontocerebellar) and atroph*).hw.
77	(shy-drager syndrome* or striatonigral degenerat* or batten* disease?).ti,ab.
78	(shy-drager syndrome* or striatonigral degenerat* or batten* disease?).hw.
79	(progressive adj1 supranuclear adj1 pals*).ti,ab.
80	(progressive and supranuclear and pals*).hw.
81	(richardson* adj1 (disease? or syndrome?)).ti,ab.
82	(richardson* and (disease? or syndrome?)).hw.
83	((corticobasal or cortico basal) adj1 degenerat*).ti,ab.
84	((corticobasal or cortico basal) and degenerat*).hw.
85	(white adj1 matter adj1 disorder?).ti,ab.
86	(white and matter and disorder?).hw.
87	(metachromatic leukodystroph* or mitochondrial myopath* or mucopolysaccharidos*).ti,ab.
88	(metachromatic leukodystroph* or mitochondrial myopath* or mucopolysaccharidos*).hw.
89	(lysosomal adj1 storage adj1 disorder?).ti,ab.
90	(lysosomal and storage and disorder?).hw.
91	((genetic or William* or catch-22 or rett* or congenital or f?etal alcohol) adj1 (syndrome or disorder*)).ti,ab.
92	((genetic or William* or congenital or f?etal alcohol) and (syndrome or disorder*)).hw.
93	(perinatal illness* or perinatal hypoxia*).ti,ab.
94	(perinatal illness* or perinatal hypoxia*).hw.

#	Searches
95	(primary adj1 dystonia?).ti,ab.
96	(primary and dystonia?).hw.
97	(heredit* adj1 motor* adj1 sens* adj1 neuropath*).ti,ab.
98	(heredit* and motor* and sens* and neuropath*).hw.
99	(spina bifida? or spinal dysraphism?).ti,ab.
100	(spina bifida? or spinal dysraphism?).hw.
101	((functional* or psychogenic* or dissociative*) adj1 neurologic* adj1 (disorder* or dysfunction* or difficult*)).ti,ab.
102	((functional* or psychogenic* or dissociative*) and neurologic* and (disorder* or dysfunction* or difficult*)).hw.
103	((movement* or motor* or convers*) adj1 (disorder* or dysfunct*)).ti,ab.
104	((movement* or motor* or convers*) and (disorder* or dysfunct*)).hw.
105	((psychogenic or dissociative or non-epilep* or nonepilep*) adj1 (seizure* or convulsion* or fit or fits or spasm* or attack*)).ti,ab.
106	((psychogenic or dissociative or non-epilep* or nonepilep*) and (seizure* or convulsion* or fit or fits or spasm* or attack*)).hw.
107	(pseudo-seizure* or pseudoseizure*).ti,ab.
108	(pseudo-seizure* or pseudoseizure*).hw.
109	(medical* adj1 (unexplain* or un-explain*) adj1 symptom?).ti,ab.
110	(medical* and (unexplain* or un-explain*) and symptom?).hw.
111	or/1-110
112	fatig*.ti,ab.
113	fatig*.hw.
114	(lassitude or brain fog* or tired* or exhaustion or exhausted or abulia or akinesia).ti,ab.
115	(lassitude or brain fog* or tired* or exhaustion or exhausted or abulia or akinesia).hw.
116	(cloud* adj3 conscious*).ti,ab.
117	(cloud* and conscious*).hw.
118	letharg*.ti,ab.
119	letharg*.hw.
120	apath*.ti,ab.
121	apath*.hw.
122	asthenia.ti,ab.
123	asthenia.hw.
124	neurasthenia.ti,ab.
125	neurasthenia.hw.
126	or/112-125
127	111 and 126
128	limit 127 to yr="2013 -Current"

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Table 4: Evidence tables

Carter, 2014

Bibliographic Reference	Carter, A; Daley, A; Humphreys, L; Snowdon, N; Woodroofe, N; Petty, J; Roalfe, A; Tosh, J; Sharrack, B; Saxton, J M; Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial.; Multiple sclerosis (Houndmills, Basingstoke, England); 2014; vol. 20 (no. 8); 1112-22

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	March 2009 - August 2012
Inclusion criteria	- Clinical diagnosis of multiple sclerosis (MS), as defined by the modified McDonald criteria, with an Expanded Disability Status Scale (EDSS) score of 1.0–6.5, and able to walk a 10-metre distance, - Aged 18–65 years, - Clinically stable for at least four weeks prior to entering the study, - Physically able to participate in exercise three times per week, - Able to provide written informed consent, - Participants on disease-modifying therapy (interferon beta, glatiramer acetate and natalizumab) had been stable on this treatment for at least three months.
Exclusion criteria	- Comorbid conditions impairing the ability to be physically active three times per week,

	- Unwilling to be randomised, - Living more than 20 miles from the trial centre, - Already engaged in structured exercise or brisk walking ≥3 times per week for ≥30-minutes per session for at least 6 months.
Patient characteristics	N=120 adults with multiple sclerosis. EXIMS intervention plus usual care n=60. Usual care n=60. Age in years [Mean (SD)]: - EXIMS intervention plus usual care: 45.7 (9.1) - Usual care: 46.0 (8.4) Sex (M/F): - EXIMS intervention plus usual care: n=17/n=43 - Usual care: n=17/n=43 Time since diagnosis in years [Mean (SD)]: - EXIMS intervention plus usual care: 8.4 (7.4) - Usual care: 9.2 (7.9) Chronic neurological disorder category: Progressive neurological disease.
Intervention(s)/control	**Intervention** Name: EXercise Intervention for people with MS (EXIMS) programme Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management.

	Delivery setting: University exercise research facility and home Number/frequency of sessions: Weeks 1-6: 2x 1-hour (maximum) supervised sessions at the centre and 1 self-directed exercise session at home every week. Weeks 7-12: 1 supervised session at the centre and 2 self-directed exercise sessions at home every week. Duration: 12 weeks Practitioner: Physiotherapist and an exercise physiologist The supervised exercise sessions incorporated cognitive-behavioural techniques (such as goal setting, finding social support, understanding the costs/benefits of exercise) to promote long-term participation in physical activity. The cognitive-behavioural elements were integrated into the exercise sessions using strategies appropriate to the conversation, stage of change and concerns/questions raised by participants. **Control** Name: Usual care Protocol description: Control (usual care) Delivery setting: Not applicable Number/ frequency of sessions: Participants in the usual care group were offered three exercise sessions at the university exercise research facility and individual exercise advice after the study. Duration: Not applicable. Practitioner(s): Not applicable Usual care continued to receive any concomitant care they were already receiving, with no additional treatment. Participants in the usual care group were offered 3 exercise sessions at the university exercise research facility and individual exercise advice after the study.
Duration of follow-up	6-months post-intervention
Sources of funding	Not industry funded

Sample size	N=120 - EXIMS: n=60 - Usual care: n=60

EXIMS: exercise intervention for people with MS; N/n: number of participants; SD: standard deviation

Outcomes

Study timepoints

- Baseline
- Post-intervention (12 weeks from baseline)
- 6 months post-intervention

EXIMS versus usual care: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by MFIS - Polarity - Lower values are better

Outcome	EXIMS, post-intervention, N =54	EXIMS, 6-months post-intervention, N =49	Usual care, post-intervention, N =53	Usual care, 6-months post-intervention, N =50
MFIS change in score from baseline Mean (SD)	-9.2 (12.5)	-5.4 (11.89)	0.4 (11.76)	-1.5 (12.54)

EXIMS: exercise intervention for people with MS; MFIS: modified fatigue impact scale; N/n: number of participants; SD: standard deviation

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Treatment allocation was concealed from the study researchers by using a distant randomisation service at the University of York, UK. Baseline characteristics balanced at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analyses were used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(9% and 8% of participants in the intervention and control groups, respectively were lost to follow-up at the final assessment time-point; all results were biased by missing data; loss to follow-up balanced between groups so missingness does not depend on true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: MFIS. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

ITT: intention-to-treat; MFIS: modified fatigue impact scale; RCT: randomised controlled trial

Hersche, 2019

Bibliographic Reference	Hersche, R.; Weise, A.; Michel, G.; Kesselring, J.; Bella, S.D.; Barbero, M.; Kool, J.; Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: Feasibility of a randomized clinical trial; Multiple Sclerosis and Related Disorders; 2019; vol. 35; 26-33

Study details

Country/ies where study was carried out	Switzerland
Study type	Randomised controlled trial (RCT)
Study dates	August - November 2017
Inclusion criteria	- >18 years of age, - Confirmed diagnosis of MS according to the McDonald criteria, - Fatigue Severity Scale score >4, - Expanded Disability Status Scale (EDSS) score ≤6.5.
Exclusion criteria	- Telephone-based Mini Mental state Examination score <21 and Beck Depression Inventory-fast 2 screening score >4.
Patient characteris-tics	N=47 adults with multiple sclerosis. IEME + rehabilitation as usual n=24. PMR + rehabilitation as usual n=23Age in years [Mean (SD)]: - IEME + rehabilitation as usual: 51.2 (1.7) - PMR + rehabilitation as usual: 51.8 (2.2) Sex (M/F):

	- IEME + rehabilitation as usual: n=8/n=16 - PMR + rehabilitation as usual: n=8/n=15 Time since diagnosis in years [Mean (SD)]: - IEME + rehabilitation as usual: 13.5 (10.2) - PMR + rehabilitation as usual: 14.3 (9.8) Chronic neurological disorder category: Progressive neurological disease
Intervention(s)/control	**Intervention** Name: Inpatient energy management education (IEME) + rehabilitation as usual (RAU) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Inpatient rehabilitation centre Number/frequency of sessions: Sessions of 6.5-hours in duration over a 3-week period. The IEME started with a 1-hour individual session, followed by 5x 1-hour self-contained IEME group sessions (minimum 2, maximum 7 participants) delivered 2x per week, and it concluded with 0.5-hour individual sessions Duration: 3 weeks Practitioner: IEME delivered by a trained OT and RAU by multidisciplinary team IEME participants received fatigue management group-based education during the experimental intervention and that they attended individual OT sessions only for other issues. Participants acquired knowledge and understanding about factors that influence energy and the consequences of fatigue on their habits and lifestyle. Subsequently, they identified and implemented tailored behaviour modification. Between the IEME sessions, the participants received training regarding the use of energy conservation strategies and planned the implementation of behavioural changes in their daily routine using self-training tasks. Six weeks after returning home, the participants received reinforcement in the form of a letter. The treatment manual describes every session in detail, integrating the behavioural change techniques that can be used. The participant workbook contains detailed information on all topics, worksheets, and self-training tasks.

	Control Name: Muscle relaxation (PMR) and RAU Protocol description: Uni modal (physical or psychological) rehabilitation interventions for fatigue management. Delivery setting: Inpatient rehabilitation centre Number/ frequency of sessions: 6x 1-hour face-to-face group sessions of PMR (maximum 12 participants) Duration: 3 weeks Practitioner(s): PMR delivered by physical therapist and RAU by multidisciplinary team PMR involves a standardised series of relaxation exercises (involving 11 large muscle groups) combined with deep breathing. During the PMR sessions, the participants lay on the floor in a quiet room and were instructed by a trained physical therapist for 1-hour. They were also encouraged to continue to perform the PMR exercises after discharge from the clinic. At 3 weeks after discharge, a reinforcement letter was sent to all control participants, to foster continuation of the PMR exercises. All participants took part in the RAU program. This individualized program included physiotherapy (endurance and reinforcement training), occupational therapy (ability and adaptation training), speech therapy, neuropsychological training, and counselling (involving a physician and/or social worker), if relevant. The difficulties due to fatigue were discussed in individual OT sessions but no systematic fatigue management education was provided as part of RAU.
Duration of follow-up	4-months
Sources of funding	Not industry funded
Sample size	N=47 - IEME + rehabilitation as usual: n=24 - PMR + rehabilitation as usual: n=23

IEME: inpatient energy management education; N/n: number of participants; OT: occupational therapy; PMR: progressive muscle relaxation; SD: standard deviation; RAU: rehabilitation as usual

Outcomes

Study timepoints

- Baseline
- Post-intervention (3 weeks from baseline)
- 3 months post-intervention

IEME + rehabilitation as usual versus PMR + rehabilitation as usual: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by MFIS - Polarity - Lower values are better

Outcome	IEME + rehabilitation as usual, post-intervention, N = 22	IEME + rehabilitation as usual, 3-months post-intervention, N = 18	PMR + rehabilitation as usual, post-intervention, N = 18	PMR + rehabilitation as usual, 3-months post-intervention, N = 17
MFIS change in score from baseline Mean (95% CI)	-15.6 (-23.3 to -7.8)	-12.4 (-20 to -4.8)	-10.6 (-18.6 to -2.7)	-7.4 (-14 to -0.8)

IEME: inpatient energy management education; N/n: number of participants; PMR: progressive muscle relaxation; MFIS: modified fatigue impact scale

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computerised random number generation. A blinded statistician prepared consecutively numbered opaque envelopes. No significant differences in baseline characteristics.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(25% and 26% of participants in the intervention and control groups, respectively were lost to follow-up at the final assessment time-point; all results were biased by missing data; loss to follow-up balanced between groups so missingness does not depend on true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: MFIS. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

MFIS: modified fatigue impact scale

Louie, 2022

Bibliographic Reference	Louie, J.; Baquie, K.; Offerman, J.; Granger, C.L.; Khan, F.; Bower, K.J.; Maximising Abilities, Negotiating and Generating Exercise options (MANAGE) in people with multiple sclerosis: A feasibility randomised controlled trial; Clinical rehabilitation; 2022; vol. 36 (no. 4); 498-510

Study details

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT)
Study dates	October 2013 - October 2014
Inclusion criteria	- Over 18 years of age, - Diagnosis of multiple sclerosis by a medical practitioner, with an Extended Disability Status Scale 0-6.5, - Residing within the catchment area of the service, - Currently not receiving or wait-listed for outpatient physical therapies, - English at a level allowing participation.
Exclusion criteria	Individuals were excluded if they were medically unstable or had another medical condition that would preclude involvement in the program.
Patient characteristics	N=23 adults with multiple sclerosis. MANAGE programme n=12. Waitlist control n=11. Age in years [Mean (SD)]: - MANAGE programme: 48.3 (14.1)

	- Waitlist control: 8.3 (14.1) Sex (M/F): - MANAGE programme: n=6/n=6 - Waitlist control: n=4/n=7 Time since diagnosis in years [Mean (SD)]: - MANAGE programme: 12.5 (9.5) - Waitlist control: 12.1 (10.4) Chronic neurological disorder category: Progressive neurological disease
Intervention(s)/control	**Intervention** Name: MANAGE programme (self-management programme focusing on education, exercise and community integration, supported by behaviour change techniques) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Outpatient clinic (initial 6 weeks) and community (last 6 weeks) Number/frequency of sessions: 2x 60-minute sessions per week of exercise and 1x 60-minute education sessions per week for first 6 weeks in outpatient clinic; community supported sessions for last 6 weeks. Duration: 12 weeks Practitioner: Physiotherapist and an exercise physiologist Initial 6-weeks: The education sessions incorporated key behaviour change techniques including social support, goal setting and problem solving. The exercise sessions involved an individualised program based on a physiotherapy assessment completed between the initial study recruitment and week 1 of the program completed in a group setting. These exercises were prescribed after joint discussion from the physiotherapist and exercise physiologist facilitators following analysis of assessment findings and patient identified goals. Participants began with a core set of 6-8 exercises and progressed to a maximum of 10 or 12 exercises depending on their individual stamina.

	Last 6-weeks: The final 6 weeks of the program focused on community integration and sustaining exercise behaviours. Week 7 involved two supervised group exercise sessions in the community, in locations that were consensus agreed upon by participants (for example, a local gym, or tai chi group). Week 8 was an individual community exercise option visit with a facilitator as a result of participant selection following education session 5. Support and education for the community fitness trainers was provided during that session by the facilitator when there were knowledge gaps identified in the following areas: understanding multiple sclerosis and the impacts on the participant, participant goals and physical areas to address, and participant's physical limitations for monitoring and exercise titration. In weeks 9-12 participants were encouraged to attend their community exercise option independently for a minimum of once weekly and had telephone support from the facilitators if needed. **Control** Name: Waitlist control Protocol description: Control (waitlist) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): Not applicable The waitlist control group were instructed to continue with their usual activities, which did not involve outpatient physiotherapy intervention and were offered the opportunity to participate in a program after study completion.
Duration of follow-up	12-weeks post-intervention (24-weeks follow up)
Sources of funding	Not industry funded
Sample size	N=23 MANAGE programme: n=12 Waitlist control: n=11

MANAGE: maximising abilities, negotiating and generating exercise options; N/n: number of participants; SD: standard deviation

Outcomes

Study timepoints

- Baseline
- Post-intervention (12 weeks from baseline)
- 12-weeks post-intervention

MANAGE programme versus waitlist control: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by FSS - Polarity - Lower values are better

Outcome	MANAGE, post-intervention, N =9	MANAGE, 12-weeks post-intervention, N =10	Waitlist control, post-intervention, N =8	Waitlist control, 12-weeks post-intervention, N =5
FSS change in score from baseline Mean (95% CI)	-0.53 (-1.12 to 0.06)	-0.43 (-1.12 to 0.26)	-0.02 (-0.68 to 0.64)	1.24 (-0.35 to 2.83)

CI: confidence interval; FSS: fatigue severity scale; MANAGE: maximising abilities, negotiating and generating exercise options; N/n: number of participants

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Internet-based random number generator. Sequentially numbered, sealed opaque envelopes with allocation. There were no significant differences between the two*

Section	Question	Answer
		groups in baseline characteristics or outcome measures, except for an increased use of gait aids in the intervention group.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. No details if ITT analyses performed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(17% and 45% of participants in the intervention and control groups, respectively were lost to follow-up at the final assessment time-point with no methods to control for missing data; all results were biased by missing data; loss to follow-up not balanced between groups so missingness may depend on true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: FSS. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

FSS: fatigue severity scale; ITT: intention-to-treat

Nguyen, 2017

Bibliographic Reference	Nguyen, S.; McKay, A.; Wong, D.; Rajaratnam, S.M.; Spitz, G.; Williams, G.; Mansfield, D.; Ponsford, J.L.; Cognitive Behavior Therapy to Treat Sleep Disturbance and Fatigue After Traumatic Brain Injury: A Pilot Randomized Controlled Trial; Archives of Physical Medicine and Rehabilitation; 2017; vol. 98 (no. 8); 1508-1517e2

Study details

Country/ies where study was carried out	Australia
Study type	Randomised controlled trial (RCT)
Study dates	March 2013 - September 2015
Inclusion criteria	Aged 16 to 65 years with documented mild to severe traumatic brain injury (TBI) as defined by external impact to the head resulting in at least one of the following: - Confusion or disorientation, - Loss of consciousness, - Posttraumatic amnesia, - Other neurologic abnormalities or intracranial lesion. Candidates must have self-reported poor sleep (Pittsburgh Sleep Quality Index [PSQI] score >5) and/or fatigue (Fatigue Severity Scale [FSS] score 4).
Exclusion criteria	Presence of other neurologic disorders, acute psychiatric symptoms, or substance abuse and transmeridian travel or night shift work in the 4 weeks preceding baseline assessment. Individuals screening as high risk on the Berlin Questionnaire were examined by a sleep physician to exclude for sleep apnoea.
Patient characteristics	N=24 adults with traumatic brain injurty CBT + exercise: n=13

	Treatment as usual: n=11 Age in years [Mean (SD)]: - CBT + exercise: 45.53 (13.87) - Treatment as usual: 41.90 (12.95) Sex (M/F): - CBT + exercise: n=9/n=4 - Treatment as usual: n=4/n=7 Time since injury in days [Mean (SD)]: - CBT + exercise: 795.15 (714.23) - Treatment as usual: 2093.36 (2192.62) Chronic neurological disorder category: Acquired brain injury
Intervention(s)/control	**Intervention** Name: Cognitive behaviour therapy + exercise Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Not reported Number/frequency of sessions: The treatment comprised 6 modules addressing sleep and fatigue across 8 sessions plus as part of behaviour activation, 3-5x 30-minutes of moderate exercise sessions per week Duration: Not reported Practitioner: Clinical neuropsychologists with advanced training in CBT and exercise physiologist

	The intervention was standardized using a study-specific manual. The manualized intervention included core CBT principles of psychoeducation, behavioural activation, behaviour experiments, modification of un-helpful thinking styles, problem-solving, relaxation, and relapse prevention. As part of behaviour activation, participants were assessed by an exercise physiologist to determine safe exercise guidelines. A target heart rate training range (60%-80% of predicted maximum heart rate) was given to each participant to encourage participation in regular exercise, aiming for 30-minutes of moderate exercise 3-5x per week, wearing a heart rate monitor. Exercise output was monitored using a pedometer measuring distance walked. **Control** Name: Treatment as usual Protocol description: Control (treatment as usual) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): Not applicable In both groups, participants were permitted to continue TAU, which typically included occupational therapy, physiotherapy, pharmacotherapy, and psychotherapy for mood. TAU participants were offered the CBT intervention on completion of the 4-month follow-up period.
Duration of follow-up	4-months
Sources of funding	Not industry funded
Sample size	N=24 - CBT + exercise: n=13 - Treatment as usual: n=11

CBT: cognitive behaviour therapy; N/n: number of participants; SD: standard deviation; TAU: treatment as usual

Outcomes

Study timepoints

- Baseline
- 4-months

CBT + exercise versus treatment as usual: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by BFI - Polarity - Lower values are better

Fatigue severity or impact on fatigue as measured by FSS - Polarity - Lower values are better

Outcome	CBT + exercise, 4-months, N =13	Treatment as usual, 4-months, N = 11
BFI change in score from baseline Mean (SE)	-1.22 (1.44)	0.22 (0.2)
FSS change in score from baseline Mean (SE)	-0.15 (0.05)	0.53 (0.2)

BFI: brief fatigue inventory; CBT: cognitive behaviour therapy; FSS: fatigue severity scale; N/n: number of participants; SE: standard efficient

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was performed with an online random number sequence generator and transcribed into allocation sequences. There were no significant*

Section	Question	Answer
		group differences in participant demographics, injury variables, and clinical characteristics at baseline.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analyses were used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All participants randomised were analysed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: BFI; FSS. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

BFI: brief fatigue inventory; FSS: fatigue severity scale; ITT: intention-to-treat

Patt, 2023

Bibliographic Reference	Patt, N.; Kupjetz, M.; Kool, J.; Hersche, R.; Oberste, M.; Joisten, N.; Gonzenbach, R.; Nigg, C.R.; Zimmer, P.; Bansi, J.; Effects of inpatient energy management education and high-intensity interval training on health-related quality of life in persons with multiple

sclerosis: A randomized controlled superiority trial with six-month follow-up; Multiple Sclerosis and Related Disorders; 2023; vol. 78; 104929

Study details

Country/ies where study was carried out	Switzerland
Study type	Randomised controlled trial (RCT)
Study dates	13 July 2020 - 19 October 2021
Inclusion criteria	- Age >18 years; - Multiple sclerosis (MS) diagnosis (revised McDonald criteria Thompson et al. 2018) with relapsing-remitting, primary or secondary progressive MS phenotypes, - Expanded Disability Status Scale (EDSS) score ≤6.5, - Fatigue Scale for Motor and Cognitive Functions (FSMC) total score ≥43, - Literacy and understanding in German.
Exclusion criteria	- Cognitive impairment (22-point Mini-Mental State Examination score (MMSE) <21, - Hospital Anxiety and Depression Scale (HADS) depression subscale >11, - Concomitant cardiopulmonary or other neurodegenerative diseases in addition to MS, - Infections; pregnancy/intention to become pregnant, - Stem cell treatment within the last 6 months, - Previous participation in an IEME or HIIT study.
Patient characteristics	N=106 adults with multiple sclerosis.

	IEME + HIIT n=53. PMR + MCT n=53. Age in years [Mean (SD)]: - IEME + HIIT: 49.98 (10.90) - PMR + MCT: 49.51 (8.81) Sex (M/F): - IEME + HIIT: n=19/n=34 - PMR + MCT: n=16/n=37 Time since diagnosis in years [Mean (SD)]: - IEME + HIIT: 15.02 (9.35) - PMR + MCT: 11.79 (8.37) Chronic neurological disorder category: Progressive neurological diseases
Intervention(s)/control	All participants underwent a 3-week multidisciplinary inpatient rehabilitation programme, comprising physiotherapy to improve balance and walking ability (5x 30–60 minutes per week), strength training (3x 30–45-minutes per week), occupational therapy focusing on ADL (2-3x 30-minutes per week), neuropsychology addressing cognitive deficits (2x 30-minutes per week), social counselling and regular consultations with a physician, tailored to the individual needs of the patient. **Intervention** Name: Inpatient energy management education (IEME) + high-intensity interval training (HIIT) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management. Delivery setting: Inpatient rehabilitation stay

	Number/frequency of sessions: IEME: Started with a 1:1 individual 1-hour session, subsequently, they participated in 5x 1-hour group sessions, and an individual 30-minute session. HIIT: 5x 1.5-minute high-intensive intervals twice-weekly. Duration: 3 weeks Practitioner: Multidisciplinary **Control** Name: Progressive muscle relaxation (PMR) + moderate continuous training (MCT) Protocol description: Uni modal (physical or psychological) rehabilitation interventions for fatigue management. Delivery setting: Inpatient rehabilitation stay Number/ frequency of sessions: PMR: 6x 1-hour group sessions. MCT: Participants cycled continuously for 24-minutes twice-weekly Duration: 3 weeks Practitioner(s): Multidisciplinary team “Booster” was sent to all participants 6 weeks after discharge to remind them of the individual goals set at the end of their 3-week inpatient rehabilitation stay. Participants were reinforced to continue exercising (EG, UC), apply energy conservation strategies (EG), and performing PMR exercises (UC).
Duration of follow-up	6-months
Sources of funding	Not industry funded
Sample size	N=106 - IEME + HIIT: n=53 - PMR + MCT: n=53

HIIT: high-intensity interval training; IEME: inpatient energy management education; MCT: moderate continuous training; N/n: number of participants; PMR: progressive muscle relaxation; SD: standard deviation

Outcomes

Study timepoints

- Baseline
- Post-intervention (3 weeks from baseline)
- 4 months post-intervention
- 6 months post-intervention

IEME + HIIT versus PMR + MCT: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by FSMC - Polarity - Lower values are better

Outcome	IEME + HIIT, post-intervention, N =53	IEME + HIIT, 4-months post-intervention, N =53	IEME + HIIT, 6-months post-intervention, N =53	PMR + MCT, post-intervention, N =53	PMR + MCT, 4-months post-intervention, N =53	PMR + MCT, 6-months post-intervention, N =53
FSMC change in score from baseline Mean (SD)	-5.02 (11.12)	-2.78 (11.96)	-1.67 (10.91)	-4.3 (10.02)	-1.54 (11.71)	-0.46 (10.79)

FSMC: fatigue scale for motor and cognitive functions; HIIT: high-intensity interval training; IEME: inpatient energy management education; MCT: moderate continuous training; N/n: number of participants; PMR: progressive muscle relaxation; SD: standard deviation

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Random computer sequence and concealed allocation. No significant baseline differences reported, no p-value to support this.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analyses were used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All randomised participants analysed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: FSMC. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants/carer aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

FSMC: fatigue scale for motor and cognitive functions; ITT: intention-to-treat

Rietberg, 2014

Bibliographic Reference	Rietberg, M.B.; Van Wegen, E.E.H.; Eyssen, I.C.J.M.; Kwakkel, G.; Effects of multidisciplinary rehabilitation on chronic fatigue in multiple sclerosis: A randomized controlled trial; PLoS ONE; 2014; vol. 9 (no. 9); e107710

Study details

Country/ies where study was carried out	Netherlands
Study type	Randomised controlled trial (RCT)
Study dates	January 2006 - December 2009
Inclusion criteria	- Older than 18 years, - Diagnosed with MS according to the McDonald criteria, - Suffering from chronic fatigue according to the MSCCPG definition, - Able to walk.
Exclusion criteria	- Current MS relapse, - Pregnancy, - Current infection (cystitis), - Alcohol or substance abuse, - Physical conditions like muscle spasm or pain contributing to sleep problems, - Pharmacological treatment for fatigue that was started in the past 3 months, - Depressive symptomatology importantly contributing to fatigue according to the Hospital Anxiety and Depression Scale (HADS). A score of 8 or higher on the depression scale was classified as depression.

Patient characteristics	N=50 adults with multiple sclerosis. Multidisciplinary Rehabilitaiton programme: n=25. MS nurse: n=25. Age in years [Mean (SD)]: - Multidisciplinary Rehabilitation programme: 45 (9.9) - MS Nurse: 47 (8.6) Sex (M/F): - Multidisciplinary Rehabilitation programme: n=9/n=14 - MS Nurse: n=8/n=17 Time since diagnosis in years [Mean (SD)]: - Multidisciplinary Rehabilitation programme: 7 (6.6) - MS Nurse: 8 (6.1) Chronic neurological disorder category: Progressive neurological diseases
Intervention(s)/control	**Intervention** Name: Multidisciplinary Rehabilitation programme (MDR) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Outpatient clinic Number/frequency of sessions: 2x 45-minute supervised aerobic exercise per week; 1-hour occupational therapy session (with follow-up); 1-hour social work session (with follow-up) Duration: 12 weeks

	Practitioner: Occupational therapist, physiotherapist, social worker Patients assigned to MDR received an individually tailored programme that focussed on optimising self-management behaviour in daily life activities on the domains of physical fitness, behaviours or cognitions that perpetuate fatigue, and energy conservation. For addressing these therapy goals participants received physical therapy, or occupational therapy, or social work, or any combination of these treatments. For PT, the number of treatment sessions was predefined, whereas for the other intervention types, the number of sessions was on an as-needed basis, with a minimum of 2 sessions. In addition to the outpatient treatment sessions, the MS patients were given homework assignments. Physical therapy: An individualized exercise training program was devised to address the 'reconditioning' factor, aimed at improving physical fitness. Occupational therapy: Patients were referred to occupational therapy to address the factors of 'dividing time between rest and activity', 'work, education, leisure time and social contacts', 'sitting and walking' and 'personal care'. During a 1-hour session, intervention goals were set, which were evaluated in follow-up consultations. Fatigue management skills were taught to help with the application of coping strategies, energy conservation, time management, efficient body mechanics and task performance. Social work: Patients were referred to social work to address the factors of 'support from the environment', 'conflicts at work or with social services', and 'coping with MS'. The social worker provided psychosocial support through counselling and practical assistance. Goals were set during a 1-hour session, and subsequently evaluated in follow up consultations. The psychosocial support, used the techniques of skilled listening, encouragement to ventilate feelings, normalization of feelings and advice regarding coping strategies, coupled with practical help to enable both patient and family to cope with difficult circumstances identified. **Control** Name: MS Nurse Consultation Protocol description: Control (usual care) Delivery setting: outpatients Number/ frequency of sessions: 1-hour session and subsequent follow-up consultation every 3 weeks. Duration: 12-weeks Practitioner(s): MS nurse

	Patients allocated to the MS nurse group received consultation according to the Nursing Intervention Classification. Goals were set during a 1-hour session, and subsequently evaluated in follow-up consultations every three weeks. The nurse discussed general principles of planning of activities, priority setting, energy conservation, accepting help from others with daily life activities or use of devices. Physical activity was recommended. Patients were advised on nutrition and alcohol and drug intake. In addition to the consultation sessions, the patients were given homework assignments.
Duration of follow-up	24 weeks
Sources of funding	Not industry funded
Sample size	N=48 Multidisciplinary Rehabilitation programme: n=23 MS nurse: n=25

MS: multiple sclerosis; MDR: multidisciplinary rehabilitation programme; MSCCPG: multiple sclerosis council for clinical practice guidelines; N/n: number of participants; PT: physical therapy; SD: standard deviation

Outcomes

Study timepoints

- Baseline
- Post-intervention (12 weeks from baseline)

Multidisciplinary Rehabilitation programme versus MS nurse: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by CIS-20R - Polarity - Lower values are better

Outcome	**Multidisciplinary Rehabilitation programme, post-intervention, N=21**	**MS nurse, post-intervention, N =23**
CIS-20R change in score from baseline	-0.8 (7.1)	2.2 (10.3)

Outcome	Multidisciplinary Rehabilitation programme, post-intervention, N=21	MS nurse, post-intervention, N =23
Mean (SD)		

CIS-20R: checklist individual strength–20 item; N/n: number of participants; SD: standard deviation

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The randomisation procedure was concealed and based on computer-generated block randomisation. No significant differences in baseline characteristics.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. No information if ITT performed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(9% and 8% of participants in the intervention and control groups, respectively were lost to follow-up at the final assessment time-point; all results were biased by missing data; loss to follow-up balanced between groups so missingness unlikely depended on true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: CIS-20R. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

CIS-20R: checklist individual strength–20 item; ITT: intention-to-treat

Ryan, 2020

Bibliographic Reference	Ryan, J.M.; Fortune, J.; Stennett, A.; Kilbride, C.; Lavelle, G.; Hendrie, W.; DeSouza, L.; Abdul, M.; Brewin, D.; David, L.; Anokye, N.; Victor, C.; Norris, M.; Safety, feasibility, acceptability and effects of a behaviour-change intervention to change physical activity behaviour among people with multiple sclerosis: Results from the iStep-MS randomised controlled trial; Multiple Sclerosis Journal; 2020; vol. 26 (no. 14); 1907-1918

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	April - September 2017
Inclusion criteria	- Self-reported diagnosis of multiple sclerosis (MS); this method of identifying a diagnosis of MS is consistent with the method used in the MS Therapy Centre, which is the site for this trial. - Relapse free for the past 3 months; a relapse will be defined as 'the appearance of new symptoms, or the return of old symptoms, for a period of 24-hours or more, in the absence of a change in core body temperature or infection'. - Independently ambulatory at a minimum within their home with or without a walking aid. - Free of unstable medical conditions, for example, unstable angina. - Ability to travel to the Berkshire MS Therapy Centre for the intervention. - Fluent in English to a standard sufficient for completion of the trial assessment and intervention. - Able to comprehend and follow all instructions relating to participation in the study including providing informed consent, completing the outcome measures or participating in the intervention.
Exclusion criteria	- Pregnancy, - Ongoing participation in other trials

Patient characteristics	N=60 adults with multiple sclerosis. i-Step MS + usual care n=30 Usual care n=30 Age in years [Mean (SD)]: - i-Step + usual care: 56.9 (9.0) - Usual care: 56.7 (9.2) Sex (M/F): - i-Step + usual care: n=13/n=17 - Usual care: n=6/n=24 Time since diagnosis in years [Mean (SD)]: - i-Step + usual care: 16.1 (10.5) - Usual care: 13.7 (9.4) Chronic neurological disorder category: Progressive neurological diseases
Intervention(s)/control	**Intervention** Name: i-Step + usual care Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: NHS therapy centre Number/frequency of sessions: Four physical activity sessions with behaviour change techniques (session 1+3: 45-minutes; sessions 2+4: 30-minutes) Duration: 12 weeks

	Practitioner: Physiotherapist The handbook was developed to guide physiotherapists and participants through the four physical activity sessions. It was developed by cognitive-behavioural trainers with experience in training health professionals to use brief behaviour change techniques, the research team, people with MS and experienced neurological physiotherapists. Format of the sections dedicated to each session is: overview, pre-session reading and reflection, content specific to that session (for example, barriers and facilitators to physical activity), goal setting, and a diary to record and monitor goals. Key behaviour change techniques included 'goal setting (behaviour)', 'action planning', 'barrier identification/ problem solving', 'set graded tasks', 'prompt review of behavioural goals', 'prompt self-monitoring of behaviour' and 'provide information on where and when to perform behaviour'. Participant must set a goal relating to step-count, general physical activity and sedentary behaviour, in consultation with the physiotherapist, at the end of sessions 1, 2 and 3. Participants in the intervention arm will be provided with a Yamax SW-200 digiwalker pedometer at session. The Yamax SW-200 digiwalker has strong concurrent validity in adults with MS when compared with accelerometry. Participants will be asked to wear the pedometer on their trousers or skirt at the right hip for all waking hours, except for swimming and bathing, for at least 7 days between each session. They will record their stepcount and whether they achieved their physical activity and sedentary behaviour goal for at least 1 week between each session in the handbook. **Control** Name: Usual care Protocol description: Control (usual care) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): Not applicable Participants allocated to the control group will receive ongoing usual care that could range from intensive physiotherapy to no treatment.
Duration of follow-up	9-months

Sources of funding	Not industry funded
Sample size	N=60 - i-Step MS + usual care: n=30 - Usual care: n=30

MS: multiple sclerosis; SD: standard deviation

Outcomes

i-Step + usual care versus usual care: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by MFIS - Polarity - Lower values are better

Outcome	i-Step MS, post-intervention, N =28	i-Step MS, 6-months post-intervention, N =27	Usual care, post-intervention, N =27	Usual care, 6-months post-intervention, N =25
MFIS change in score from baseline Mean (SD)	-7.9 (12.7)	-8.6 (12.7)	-3.2 (12.2)	-0.3 (12.1)

MFIS: modified fatigue impact scale; N/n: number of participants; SD: standard deviation

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer-generated random schedule in random permuted blocks of 2 or 4. The allocation sequence was placed in sequentially numbered, opaque, sealed envelopes. Baseline characteristics look sufficiently similar, although no statistical analysis done to ascertain this.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analysis were used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All randomised participants analysed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(The questionnaires used were all validated and widely used tools: MFIS. Standardised and validated measurement tools implemented by researchers aware of allocation. Outcomes self-reported by unblinded participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

ITT; intention-to-treat; MFIS: modified fatigue impact scale

Rytter, 2019

Bibliographic Reference	**Rytter, H.M.; Westenbaek, K.; Henriksen, H.; Christiansen, P.; Humle, F.; Specialized interdisciplinary rehabilitation reduces persistent post-concussive symptoms: a randomized clinical trial; Brain Injury; 2019; vol. 33 (no. 3); 266-281**

Study details

Country/ies where study was carried out	Denmark
Study type	Randomised controlled trial (RCT)
Study dates	January 2012 - August 2015
Inclusion criteria	- Have a documented commotio cerebri from a primary source, - At least 6 months postinjury, - 18 to 65 years of age, - Have experienced persistent post-concussive symptoms in the form of attention and/or memory problems combined with at least three other relevant symptoms according to the ICD-10 diagnostic criteria for post-concussion syndrome (PCS), which occurred not later than 4 weeks after the head trauma and continued for at least 6 months. - Adequate language skills in Danish to be able to take part in the rehabilitation programme. - Be clinically appropriate for either arm of treatment and capable of attending the treatment programme in its entirety with different activities and requirements. - Have a level of cognitive capabilities enabling them to function in a therapeutic group. - Can transport themselves to the rehabilitation centre.
Exclusion criteria	- Had another active, treatment-requiring illness that prevented them from fully participating in the programme (for example, cancer treatment). - History of any diagnosed psychiatric disease or had a current onset of psychiatric problems, for which they were treated by a psychiatrist. - History of or current, substance abuse, - Suffered a progressive neurodegenerative disease, - History of moderate to severe traumatic brain injury,

	- History of chronic pain and migraine.
Patient characteristics	N=89 adults with persistent post-concussive symptoms Specialised interdisciplinary rehabilitation (S-rehab) n=45 Standard care n=44 Age in years [Mean (SD) not reported] [n, 18–29 years; 30–43 years; >44 years]: - S-rehab: 12;21;12 - Standard care: 12;24;8 Sex (M/F): - S-rehab: n=16/n=29 - Standard care: n=14/n=30 Time since injury in months [Mean (SD)]: - S-rehab: 26.85 (16.30) - Standard care: 29.06 (18.11) Chronic neurological disorder category: Acquired brain injury
Intervention(s)/control	**Intervention** Name: S-rehab (comprehensive interdisciplinary rehabilitation emphasizing the integration of the different therapeutic interventions - targeting cognitive, emotional and physical domains as well as interpersonal skills within the context of a therapeutic environment) Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Small group of 6-8 at Centre for Rehabilitation of Brain Injury (CRBI)

	Number/frequency of sessions: Module 1: 12–14 individual consultation sessions with a neuropsychologist (1–2-hours per week), a total of 24-hours of group therapy (2-hours per week) combining psychoeducation, small exercises and group discussions; 33 hours (2–3-hours per week) of individual exercise training and coaching by a physiotherapist. Module 2: 10 individual consultation sessions with a neuropsychologist (1-hour per week), 16 hours of group work (1.5-hour per week), 10.5-hours of individual exercise training and coaching with a physiotherapist (1-hour per week), 1-meeting with a case manager in the participant's municipality and 2 meetings with an existing or potential employer Duration: 22 weeks [divided into 2 modules - module 1 (12 weeks) and 2 (10 weeks)] Practitioner: All the therapists at CRBI were highly skilled with a background in either neuropsychology or physiotherapy The first module focused on education, the second on return to work **Control** Name: Standard care Protocol description: Control (standard care) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): General practitioner Some participants in the standard care group received no, or a very limited, treatment funded by the municipality, while others received several therapies. Participants in the standard care group were phoned once a month by a project coordinator, who asked them about their general condition and about the treatments they were currently receiving.
Duration of follow-up	6-months post-intervention
Sources of funding	Not industry funded
Sample size	N=89 - S-rehab: n=45

	- Standard care: n=44

CRBI: Centre for Rehabilitation of Brain Injury; N/n: number of participants; SD: standard deviation; S-rehab: specialised interdisciplinary rehabilitation

Outcomes

Study timepoints

- Baseline
- Post-intervention (22 weeks from baseline)
- 6 months post-intervention

S-rehab versus standard care: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by MFI-20 - Polarity - Lower values are better

Outcome	S-rehab versus standard care, post-intervention, N=45 vs 44	S-rehab versus standard care, 6-months post-intervention, N=45 vs 44
MFI-20: general fatigue Difference between groups Hedge's g effect size (p-value)	0.43 (0.142)	0.56 (0.048[1])
MFI-20: physical fatigue Difference between groups Hedge's g effect size (p-value)	0.20 (0.097)	0.19 (0.143)
MFI-20: reduced activities Difference between groups	0.34 (0.113)	0.74 (0.002[1])

Outcome	S-rehab versus standard care, post-intervention, N=45 vs 44	S-rehab versus standard care, 6-months post-intervention, N=45 vs 44
Hedge's g effect size (p-value)		
MFI-20: reduced motivation Difference between groups Hedge's g effect size (p-value)	0.13 (0.928)	0.11 (0.126)
MFI-20: mental fatigue Difference between groups Hedge's g effect size (p-value)	0.42 (0.019[1])	0.50 (0.016[1])

MFI-20: multidimensional fatigue inventory – 20 item; N/n: number of participants; S-rehab: Specialized interdisciplinary rehabilitation
[1]Statistically significant benefit favouring S-rehab

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomization was performed as minimization using three stratification variables. The allocation of participants to treatment conditions was concealed by placing the individual randomized assignments in sealed envelopes which were sent to the participants by mail. There were no significant differences between participants in the S-REHAB and STAND group regarding age, gender, educational level and marital status.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analyses were used.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All randomised participants analysed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The questionnaires used were all validated and widely used tools: MFI-20. Standardised and validated measurement tools implemented by researchers blinded to allocation, however outcomes subjective and participants aware of allocation.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol available.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

ITT: intention-to-treat; MFI-20: multidimensional fatigue inventory–20 item; S-rehab: specialised interdisciplinary rehabilitation

Thomas, 2017

Bibliographic Reference	Thomas, S; Fazakarley, L; Thomas, PW; Collyer, S; Brenton, S; Perring, S; Scott, R; Thomas, F; Thomas, C; Jones, K; et, al.; MiivitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis; BMJ open; 2017; vol. 7 (no. 9); e016966

Study details

Country/ies where study was carried out	UK

Study type	Randomised controlled trial (RCT)
Study dates	February 2013 - July 2013
Inclusion criteria	- Clinically definite diagnosis of multiple sclerosis (MS), - Aged 18 years or above, - Satisfied a risk assessment (see below), - Relatively physically inactive (active for a period of 30min or more on fewer than 5 days per week), - Having a suitable television at home.
Exclusion criteria	- Adapted Patient Determined Disease Steps (APDDS) Scale score of 1 or ≥6 (equivalent to an Expanded Disability Status Scale score of 1 or ≥6, - A relapse within the past 3 months that required treatment with corticosteroids and/or a hospital admission, - Already participating in exercise or rehabilitation research, - A medical condition placing an individual at risk from exercise participation, - Owns a Wii and is currently using it on a weekly basis or more, - Unwilling or unable to comply with the protocol (for example, long vacation planned).
Patient characteristics	N=30 adults with multiple sclerosis Mii-vitaliSe + usual care: n=15 - Waitlist control: n=15Age in years [Mean (SD)]: - Mii-vitaliSe + usual care: 50.9 (8.08) - Waitlist control: 47.6 (9.26) Sex (M/F): - Mii-vitaliSe + usual care: n=1/n=14

	- Waitlist control: n=2/n=13 Time since diagnosis [Mean (SD) not reported] [n, <1; 1-5; 6-10; 11-15; >16 years]: - Mii-vitaliSe + usual care: 1;7;3;2;2 - Waitlist control: 2;4;4;1;4 Chronic neurological disorder category: Progressive neurological diseases
Intervention(s)/control	**Intervention** Name: Mii-vitaliSE + usual care Protocol intervention group: Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management Delivery setting: Outpatients, home, virtual, and telephone Number/frequency of sessions: Weekly modules (Week 1 and 2: Orientation to Wii; Week 3: Installation of equipment and commencement of individual programme at home; Week 5: Follow-up; Week 7: Review visit; Week 12: Follow-up; Week 16: Review visit; Week 20 and thereafter: Ongoing support) Duration: 20 weeks Practitioner: Senior physiotherapists The rationale of Mii-vitaliSe is to support people with MS to increase activity levels in their own homes using the Nintendo Wii. Mii-vitaliSe encourages the internalisation of goals, and aims to provide individuals with skills, strategies and support to identify solutions to overcome barriers they encounter. The intervention draws on relevant psychological frameworks and theories (motivational interviewing, social cognitive, cognitive behavioural and self-determination theory) and incorporates behaviour change techniques. A Mii-vitaliSe handbook provided information about the benefits of physical activity and tips and advice for using the Wii safely and maintaining a physical activity programme, including quotations from people with MS with experience of using the Wii. The intervention was personalised and this was achieved by the provision of regular one-to-one support from a physiotherapist (face-to-face and telephone) and a personal activity workbook that facilitated individualised goal setting, feedback, action and coping planning and monitoring of progress. **Control**

	Name: Waitlist control Protocol description: Control (waitlist) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): Not applicable The Dorset MS Service provides multidisciplinary support. Patients are reviewed annually by the team at an outpatient clinic or home visit appointment. On completion of the review and necessary assessments, medical and therapy treatments are delivered as required. If patients experience a deterioration of their symptoms before the next review they can self-refer to the service. Education, support and advice regarding disease modifying therapies, management of symptoms and carer support is available from the specialist nurse. The team operates a helpline service Monday to Friday and messages can be left on an answer-phone outside the scheduled helpline hours.
Duration of follow-up	6 months
Sources of funding	Not industry funded
Sample size	N=30 - Mii-vitaliSe + usual care: n=15 - Waitlist control: n=15

Mii-vitaliSe: physiotherapist-facilitated Nintendo Wii intervention package; MS: multiple sclerosis; N/n: number of participants; SD: standard deviation

Outcomes

Study timepoints

- Baseline
- 6 months post-intervention

Mii-vitaliSe + usual care versus waitlist control: Fatigue severity or impact on fatigue

Fatigue severity or impact on fatigue as measured by FSI - Polarity - Lower values are better

Outcome	Mii-vitaliSe + usual care versus waitlist control, 6 months post-intervention, N=14 vs 15
FSI ('most' fatigue item) Mean difference between groups (95% CI) Change in score from baseline	-0.36 (-1.44 to 0.73)
FSI ('least' fatigue item) Mean difference between groups (95% CI) Change in score from baseline	0.69 (-1.06 to 2.44)
FSI ('average' fatigue item) Mean difference between groups (95% CI) Change in score from baseline	0.06 (-1.26 to 1.38)
FSI ('right now' fatigue item) Mean difference between groups (95% CI) Change in score from baseline	0.20 (-1.35 to 1.75)
FSI (Interface subscale) Mean difference between groups (95% CI) Change in score from baseline	0.33 (-0.97 to 1.63)

CI: confidence interval; FSI: fatigue symptom inventory; Mii-vitaliSe: physiotherapist-facilitated Nintendo Wii intervention package; N/n: number of participants

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was carried out in a one-to-one ratio and the sequence was produced using a computer-based random sequence generator. To ensure good allocation concealment, random allocation was email-based and administered by the study statistician. Baseline characteristics of both groups look sufficiently similar, although no p-values to reinforce this.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. No information if ITT performed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(5% and 0% of participants in the intervention and control groups, respectively were lost to follow-up at the final assessment time-point; no evidence results biased by missing data.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(The questionnaires used were all validated and widely used tools: FSI. Standardised and validated measurement tools implemented by researchers aware of allocation. Outcomes self-reported by unblinded participants via post.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

FSI: fatigue symptom inventory; ITT: intention-to treat

Veenhuizen, 2019

Bibliographic Reference	Veenhuizen, Y.; Cup, E.H.C.; Jonker, M.A.; Voet, N.B.M.; Van Keulen, B.J.; Maas, D.M.; Heeren, A.; Groothuis, J.T.; Van Engelen, B.G.M.; Geurts, A.C.H.; Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial; Neurology; 2019; vol. 93 (no. 18); e1720-e1731

Study details

Country/ies where study was carried out	Netherlands
Study type	Randomised controlled trial (RCT)
Study dates	July 2014 - September 2015
Inclusion criteria	- Age 18 years or older, - Diagnosis of NMD determined by a neurologist using established criteria, - Subjective experience of chronic fatigue with a clear effect on daily life and social participation determined by an occupational therapist.
Exclusion criteria	- Major cardiorespiratory problems that precluded participation in AET, - Pregnancy, - Limited life expectancy (<5 years) due to known comorbid conditions, - Having participated in the Energetic program or a similar intervention before.
Patient characteristics	N= 53 adults with neuromuscular disease Energetic programme: n=29 Usual care: n=24 Age in years [Mean (SD) not reported] [Median (IQR)]:

	- Energetic programme: 52 (37-63) - Control: 50 (41-60) Sex (M/F): - Energetic programme: n=8/n=21 - Control: n=9/n=15 Time since diagnosis: not reported Chronic neurological disorder category: Progressive neurological disease
Intervention(s)/control	**Intervention** Name: Energetic programme (Aerobic exercise training [AET], exercise education, energy conservation management [ECM], and implementation and relapse prevention) Protocol intervention group: Interventions to support participation in recreation and leisure Delivery setting: Outpatient clinic and home Number/frequency of sessions: AET (3x 30-minute sessions per week for 16 weeks); exercise education (3x 60-minute sessions during the first 3 weeks); ECM (8x 90-minute sessions spread across the intervention period); implementation and relapse prevention (10 group sessions) Duration: 16 weeks Practitioner: Physical and occupational therapist Individually tailored AET, training intensity was aimed at 50%–70% of the maximum heart rate, based on a maximal cycling exercise test. Exercise education, patients were educated about general physical and aerobic exercise training principles in relation to NMD. ECM, education and discussion, extended by individual goal-setting, practicing activities, and performing homework activities with the aim to learn and apply energy conservation strategies in daily life. Implementation and relapse, empowered the patients with the implementation of AET and ECM in daily life, with a specific focus on finding a sustainable way to exercise at home.

	In addition, a booster session of 2-hours with the physical and occupational therapists was organized 2 months after the end of the intervention period to reinforce previously learned strategies and skills. **Control** Name: Usual Care Protocol description: Control (usual care) Delivery setting: Not applicable Number/ frequency of sessions: Not applicable Duration: Not applicable Practitioner(s): Not applicable Participants in the control group were not prescribed (or withheld) any specific intervention, which meant that some received physical therapy in primary care, other forms of multidisciplinary rehabilitation care, or no intervention at all.
Duration of follow-up	11-months post-intervention
Sources of funding	Not industry funded
Sample size	N=53 - Energetic programme: n=29 - Usual Care: n=24

AET: aerobic exercise training; ECM: energy conservation management; IQR: interquartile range; N/n: number of participants; NMD: neuromuscular disease

Outcomes

Study timepoints

- Baseline
- Post intervention (11 weeks from baseline)
- 3 months post-intervention

- 11 months post-intervention

Energetic programme versus usual care: Fatigue severity or impact on fatigue
Fatigue severity or impact on fatigue as measured by CIS-fatigue - Polarity - Lower values are better

Outcome	Energetic programme versus usual care, post-intervention, N=26 vs 22	Energetic programme versus usual care, 3-months post-intervention, N=27 vs 21	Energetic programme versus usual care, 11-months post-intervention, N=26 vs 18
CIS-fatigue Mean difference between groups (95% CI) Change in score from baseline	-2.2 (-4.7 to 0.3)	-3.9 (-8.5 to 0.8)	1.8 (-7.5 to 3.9)

CI: confidence interval; CIS-fatigue: checklist individual strength-fatigue; N/n: number of participants

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(No details on allocation concealment. Differences in baseline characteristics, however no p-value reported if statistically significant. Mean difference between energetic programme and usual care adjusted for baseline, sex, diagnosis, and work status.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Although participants and personnel were aware of interventions allocated, there were no deviations from intended interventions. ITT analysis were used.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(All randomised participants analysed.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(All outcomes (of both patients and caregivers) were assessed by blinded and independent (occupational therapy) research assistants and subsequently entered into a digital and validated database. Patients, caregivers, and therapists could not be blinded, but all participants were urged not to discuss their allocation status with the assessors. At all follow-up assessments, assessors recorded whether their blinding might have been broken.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Published protocol. Results of all analyses published in study or supplementary appendix as per protocol.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Not applicable

ITT: intention-to-treat; CIS-fatigue: checklist individual strength-fatigue

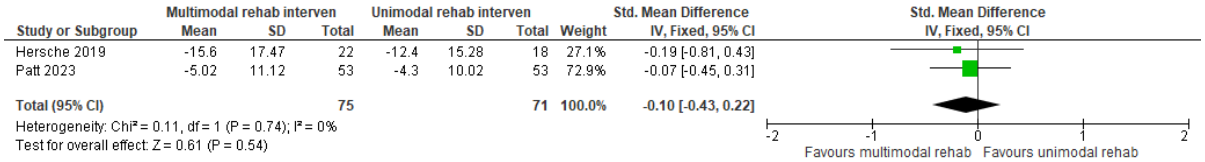
Appendix E Forest plots

Forest plots for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

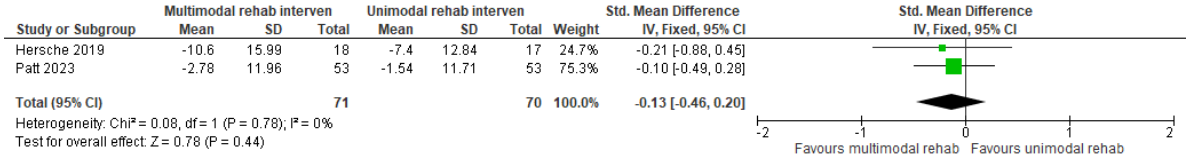
Multi modal (combined physical and psychological) rehabilitation interventions versus uni modal (physical or psychological) rehabilitation interventions in adults with multiple sclerosis

Figure 2: Fatigue as measured by a validated scale at post-intervention



Mean: mean difference between baseline and end-point
CI: confidence interval; IV: inverse variance

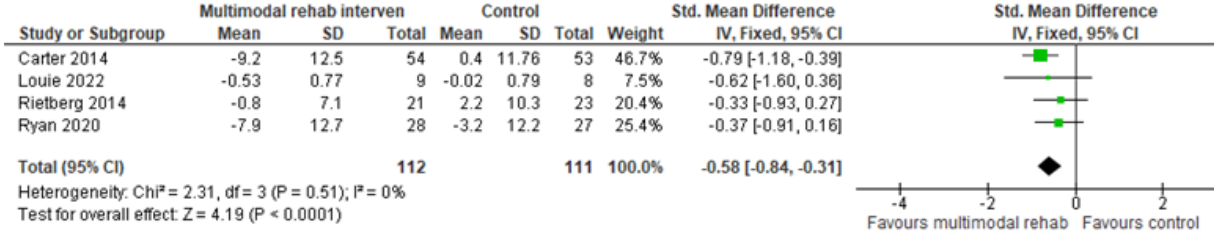
Figure 3: Fatigue as measured by a validated scale at follow-up (ranging from 3-months to 4-months)



Mean: mean difference between baseline and end-point
CI: confidence interval; IV: inverse variance

Multi modal (combined physical and psychological) rehabilitation interventions versus control in adults with multiple sclerosis

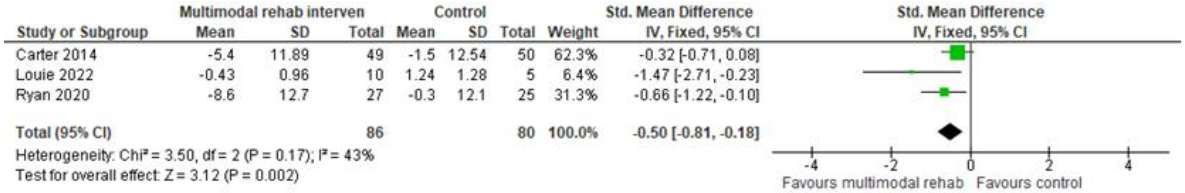
Figure 4: Fatigue as measured by a validated scale at post-intervention



Mean: mean difference between baseline and end-point

CI: confidence interval; IV: inverse variance

Figure 5: Fatigue as measured by a validated scale at follow-up (ranging from 3-months to 6-months)



Mean: mean difference between baseline and end-point

CI: confidence interval; IV: inverse variance

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Table 5: Evidence profile for comparison between multi modal (combined physical and psychological) rehabilitation interventions and uni modal (physical or psychological) rehabilitation interventions in multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi modal (combined physical and psychological) rehabilitation interventions	Uni modal (physical or psychological) rehabilitation interventions	Relative (95% CI)	Absolute		
Fatigue as measured by a validated scale at post-intervention (Better indicated by lower values)												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75	71	-	SMD 0.10 lower (0.43 lower to 0.22 higher)	LOW	CRITICAL
Fatigue as measured by a validated scale at follow-up (ranging from 3-months to 4-months post-intervention) (Better indicated by lower values)												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	70	-	SMD 0.13 lower (0.46 lower to 0.20 higher)	LOW	CRITICAL
Fatigue as measured by FSMC at 6-months (Better indicated by lower values)												
1 (Patt 2023)	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	53	-	SMD 0.11 lower (0.49 lower to 0.27 higher)	MODERATE	CRITICAL

CI: confidence interval; FSMC: fatigue scale for motor and cognitive functions; MFIS; modified fatigue impact scale; MS: multiple sclerosis; SMD: standardised mean difference
**See corresponding forest plot*
1 Very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB2
2 Serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB2

Table 6: Evidence profile for comparison between multi modal (combined physical and psychological) rehabilitation interventions and control in acquired brain injury

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi modal (combined physical and psychological) rehabilitation interventions versus control in ABI	Control	Relative (95% CI)	Absolute		
Fatigue as measured by BFI at 4-months (Better indicated by lower values)												
1 (Nguyen 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	11	-	SMD 1.54 lower (2.42 to 0.66 lower)	MODERATE	CRITICAL
Fatigue as measured by FSS at 4-months (Better indicated by lower values)												
1 (Nguyen 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	11	-	SMD 0.39 higher (0.16 lower to 0.94 higher)	LOW	CRITICAL
Fatigue as measured by MFI-20 'general fatigue' sub-scale at post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	45	44	-	Hedge's g=0.43 p-value=0.142[4]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'general fatigue' sub-scale at 6-months post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	45	44	-	Hedge's g=0.56 p-value= 0.048[5]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'physical fatigue' sub-scale at post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	45	44	-	Hedge's g=0.20 p-value= 0.097[4]	VERY LOW	CRITICAL

Fatigue as measured by MFI-20 'physical fatigue' sub-scale at 6-months post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.19 p-value= 0.143[4]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'reduced activities' sub-scale at post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.34 p-value= 0.113[4]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'reduced activities' sub-scale at 6-months post-intervention (Better indicated by lower values)												
1(Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.74 p-value= 0.002[5]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'reduced motivation' sub-scale at post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.13 p-value= 0.928[4]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'reduced motivation' sub-scale at 6-months post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.11 p-value= 0.126[4]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'mental fatigue' sub-scale at post-intervention (Better indicated by lower values)												
1 (Rytter 2019)	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.42 p-value= 0.019[5]	VERY LOW	CRITICAL
Fatigue as measured by MFI-20 'mental fatigue' sub-scale at 6-months post-intervention (Better indicated by lower values)												
1	random-ised trials	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[3]	none	45	44	-	Hedge's g=0.50 p-value= 0.016[5]	VERY LOW	CRITICAL

(Rytter 2019)												

ABI: acquired brain injury; BFI: brief fatigue inventory; CI: confidence interval; FSS: fatigue severity scale; MFI-20: multidimensional fatigue inventory-20; SMD: standardised mean difference
1 Serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB2
2 95% CI crosses 1 MID (for SMD +/-0.5)
3 Very serious imprecision in the effect estimate as study size <200
4 Differences between groups judged to be non-statistically significant according to author analysis.
5 Differences between groups judged to be statistically significant according to author analysis, favouring multi modal rehabilitation group. Clinical significance could not be determined.

Table 7: Evidence profile for comparison between multi modal (combined physical and psychological) rehabilitation interventions and control in multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multi modal (combined physical and psychological) rehabilitation interventions versus control in MS**	**Control**	**Relative (95% CI)**	**Absolute**		
Fatigue as measured by a validated scale at post-intervention (Better indicated by lower values)												
4*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	112	111	-	SMD 0.58 lower (0.84 to 0.31 lower)	VERY LOW	CRITICAL
Fatigue as measured by a validated scale at follow-up (ranging from 3-months to 6-months) (Better indicated by lower values)												
3*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	86	80	-	SMD 0.50 lower (0.81 to 0.18 lower)	VERY LOW	CRITICAL
Fatigue as measured by FSI ('most' fatigue item) at 6-months (Better indicated by lower values)												
1 (Thomas 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14	15	-	SMD 0.12 lower (1.2 lower to 0.96 higher)	VERY LOW	CRITICAL
Fatigue as measured by FSI ('least' fatigue item) at 6-months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14	15	-	SMD 0.15 higher (1.54 lower to 1.84 higher)	VERY LOW	CRITICAL

(Thomas 2017)												
Fatigue as measured by FSI ('average' fatigue item) at 6-months (Better indicated by lower values)												
1 (Thomas 2017)	random-ised trials	very se-rious[1]	no serious in-consistency	no serious in-directness	very se-rious[3]	none	14	15	-	SMD 0.017 higher (1.26 lower to 1.29 higher)	VERY LOW	CRITICAL
Fatigue as measured by FSI ('right now' fatigue item) at 6-months (Better indicated by lower values)												
1 (Thomas 2017)	random-ised trials	very se-rious[1]	no serious in-consistency	no serious in-directness	very se-rious[3]	none	14	15	-	SMD 0.05 higher (1.44 lower to 1.54 higher)	VERY LOW	CRITICAL
Fatigue as measured by FSI (Interface subscale) at 6-months (Better indicated by lower values)												
1 (Thomas 2017)	random-ised trials	very se-rious[1]	no serious in-consistency	no serious in-directness	very se-rious[3]	none	14	15	-	SMD 0.1 higher (1.14 lower to 1.33 higher)	VERY LOW	CRITICAL

CI: confidence interval; FSI: fatigue symptom Inventory; SMD: standardised mean difference
**See corresponding forest plot*
1 Very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB2
2 95% CI crosses 1 MID (for SMD +/-0.5)
3 95% CI crosses 2 MIDs (for SMD +/-0.5)

Table 8: Evidence profile for comparison between multi modal (combined physical and psychological) rehabilitation interventions and control in neuromuscular disease for fatigue

Quality assessment							No of patients		Effect		Quality	Im-portance
No of stud-ies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Impre-cision**	**Other con-siderations**	**Multi modal (combined physical and psychologi-cal) rehabilitation interventions versus control in NMD**	**Con-trol**	**Rela-tive (95% CI)**	**Absolute**		
Fatigue as measured by CIS-fatigue at post-intervention (Better indicated by lower values)												
1	random-ised trials	very se-rious[1]	no serious in-consistency	no serious indirectness	very se-rious[2]	none	26	22	-	SMD 0.48 lower (2.91 lower to 1.95 higher)	VERY LOW	CRITICAL

(Veen-huizen 2019)												
Fatigue as measured by CIS-fatigue at 3-months post-intervention (Better indicated by lower values)												
1 (Veen-huizen 2019)	random-ised trials	very se-rious[1]	no serious in-consistency	no serious indirectness	very se-rious[2]	none	27	21	-	SMD 0.46 lower (4.99 lower to 4.07 higher)	VERY LOW	CRITICAL
Fatigue as measured by CIS-fatigue at 11-months post-intervention (Better indicated by lower values)												
1 (Veen-huizen 2019)	random-ised trials	very se-rious[1]	no serious in-consistency	no serious indirectness	very se-rious[2]	none	26	18	-	SMD 0.17 lower (5.72 lower to 5.38 higher)	VERY LOW	CRITICAL

CI: confidence interval; CIS: checklist individual strength; SMD: standardised mean difference
1 Very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB2
2 95% CI crosses 2 MIDs (for SMD +/-0.5)

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Please see Supplement 2 for details on search that was undertaken and study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Ali, Arshad, Morfin, Jussely, Mills, Judith et al. (2022) Fatigue After Traumatic Brain Injury: A Systematic Review. The Journal of head trauma rehabilitation 37(4): e249-e257	- Intervention Systematic review with 21/37 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 16/37 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Alketbi, Azza, Basit, Salah, Hamza, Nouran et al. (2021) The added value of cognition-targeted exercise versus symptom-targeted exercise for multiple sclerosis fatigue: A randomized controlled pilot trial. PloS one 16(11): e0258752	- Country Study conducted in Egypt.
Anderson, Joanna K; Turner, Andy; Clyne, Wendy (2017) Development and feasibility of the Help to Overcome Problems Effectively (HOPE) self-management intervention for people living with multiple sclerosis. Disability and rehabilitation 39(11): 1114-1121	- Study design (adults) Non-randomised controlled trial in adults.
Asano, Miho and Finlayson, Marcia L (2014) Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Multiple sclerosis international 2014: 798285	- Intervention Systematic review with 19/25 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 6/25 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Bergersen, K., Halvorsen, J.O., Tryti, E.A. et al. (2017) A systematic literature review of psychotherapeutic treatment of prolonged symptoms after mild traumatic brain injury. Brain Injury 31(3): 279-289	- Country Systematic review with 4/5 studies conducted in the US, 1/5 study conducted in Europe. European study was checked against protocol criteria and was a uni-modal intervention and not multi-modal rehabilitation interventions for fatigue management.
Bisht, Babita, Darling, Warren G, Shivapour, E Torage et al. (2015) Multimodal intervention improves fatigue and quality of life in subjects with progressive multiple sclerosis: a pilot study. Degenerative neurological and neuromuscular disease 5: 19-35	- Country Study conducted in the US.
Blikman, Lyan J, Huisstede, Bionka M, Kooijmans, Hedwig et al. (2013) Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review	- Publication date Systematic review with all included studies published before 2013.

Study	Reason for exclusion
and meta-analysis. Archives of physical medicine and rehabilitation 94(7): 1360-76	
Blikman, Lyan Jm, van Meeteren, Jetty, Twisk, Jos Wr et al. (2017) Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: A randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England) 23(11): 1527-1541	- Intervention Uni-modal energy conservation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Byrnes, Keira Leigh and Whillier, Stephney (2019) Effects of Nonpharmaceutical Treatments on Symptom Management in Adults With Mild or Moderate Multiple Sclerosis: A Meta-analysis. Journal of manipulative and physiological therapeutics 42(7): 514-531	- Intervention Systematic review with 29/40 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 11/40 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Chalah, Moussa A and Ayache, Samar S (2018) Cognitive behavioral therapies and multiple sclerosis fatigue: A review of literature. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 52: 1-4	- Publication type Narrative review, not a systematic review.
Chen, Chiao-Ling, Lin, Mei-Yu, Huda, Mega Hasanul et al. (2020) Effects of cognitive behavioral therapy for adults with post-concussion syndrome: A systematic review and meta-analysis of randomized controlled trials. Journal of psychosomatic research 136: 110190	- Outcomes Systematic review with 22/24 studies reporting no relevant outcomes. Reports measures of non-fatigue related outcomes. The 2/24 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Day, Julia, Yust-Katz, Shlomit, Cachia, David et al. (2022) Interventions for the management of fatigue in adults with a primary brain tumour. The Cochrane database of systematic reviews 9: cd011376	- Intervention Systematic review with included studies checked against protocol. The 3 studies were pharmacological interventions, which are outside the protocol.
de Gier, Marieke, Beckerman, Heleen, Twisk, Jos Wr et al. (2024) Effectiveness of a blended booster programme for the long-term outcome of cognitive behavioural therapy for MS-related fatigue: A randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England) 30(1): 71-79	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
de Gier, Marieke, Beckerman, Heleen, Twisk, Jos et al. (2023) Blended versus face-to-face cognitive behavioural therapy for severe fatigue in patients with multiple sclerosis: A non-inferiority RCT. Multiple sclerosis (Houndmills, Basingstoke, England) 29(10): 1316-1326	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Elbers, Roy G, Berendse, Henk W, Kwakkel, Gert et al. (2016) Treatment of fatigue in Parkinson disease. JAMA: Journal of the American Medical Association 315(21): 2340-2341	- Intervention Systematic review with 9/11 studies investigating pharmacological interventions and not multi-modal rehabilitation interventions for fatigue management. The 2/11 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.

Study	Reason for exclusion
Folkerts, Ann-Kristin, Nielsen, Jorn, Gollan, Romina et al. (2023) Physical Exercise as a Potential Treatment for Fatigue in Parkinson's Disease? A Systematic Review and Meta-Analysis of Pharmacological and Non-Pharmacological Interventions. Journal of Parkinson's disease 13(5): 659-679	- Intervention Systematic review with 28/30 studies investigating pharmacological interventions or uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 2/30 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Franssen, M., Winward, C., Collett, J. et al. (2014) Interventions for fatigue in Parkinson's disease: A systematic review and meta-analysis. Movement disorders : official journal of the Movement Disorder Society 29(13): 1675-1678	- Publication date Systematic review with 5/14 studies published 2013 or later, and 9/14 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Garcia Jalon, E.G., Lennon, S., Peoples, L. et al. (2013) Energy conservation for fatigue management in multiple sclerosis: a pilot randomized controlled trial. Clinical rehabilitation 27(1): 63-74	- Publication date Primary study published pre-2013
Gay, M.C., Cassedanne, F., Barbot, F. et al. (2023) Long-term effectiveness of a cognitive behavioural therapy (CBT) in the management of fatigue in patients with relapsing remitting multiple sclerosis (RRMS): A multicentre, randomised, open-label, controlled trial versus standard care. Journal of Neurology, Neurosurgery and Psychiatry: jnnp-2023	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Glennon, J., Monckton, D., Faber, C.G. et al. (2018) Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. The Lancet Neurology 17(8): 671-680	- Intervention Uni-modal energy conservation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management - Only 29% of participants participated in optional graded exercise and results weren't stratified for those who participated or did not participate in exercise.
Harrison, A.M., Safari, R., Mercer, T. et al. (2021) Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. Multiple Sclerosis Journal 27(11): 1657-1678	- Intervention Network meta-analysis with 95/112 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 17/112 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Hersche, R., Roser, K., Weise, A. et al. (2022) Fatigue self-management education in persons with disease-related fatigue: A comprehensive review of the effectiveness on fatigue and quality of life. Patient Education and Counseling 105(6): 1362-1378	- Publication date Systematic review with 19/26 studies published 2013 or later, and 7/26 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Higson-Sweeney, N., Mikkola, A., Smith, L. et al. (2022) Nonpharmacological interventions for	- Population

Study	Reason for exclusion
treating fatigue in adolescents: A systematic review and narrative synthesis of randomised controlled trials. Journal of Psychosomatic Research 163: 111070	Systematic review including participants who are in protocol (6/16 studies had people with CND) and out of protocol (7/16 studies had people with chronic fatigue syndrome, 2/16 studies had people with delayed sleep phase disorder, and 1/16 study had people with a mixed population of cancer with only 10% CNS/Brain tumour). Studies including participants with CND were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Hugos, C.L., Cameron, M.H., Chen, Z. et al. (2019) A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Long-term (12-month) follow-up at one site. Multiple Sclerosis Journal 25(6): 871-875	- Country Study conducted in the US.
Hugos, C.L., Chen, Z., Chen, Y. et al. (2019) A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Short- and medium-term benefits. Multiple Sclerosis Journal 25(2): 275-285	- Country Study conducted in the US.
Hypher, R., Brandt, A.E., Skovlund, E. et al. (2022) Metacognitive Strategy Training Versus Psychoeducation for Improving Fatigue in Children and Adolescents With Acquired Brain Injuries: A Randomized Controlled Trial. Neuropsychology 36(7): 579-596	- Intervention Uni-modal metacognitive training intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Irene Renaud, M., van de Port, I.G.L., Catsman-Berrevoets, C.E. et al. (2020) Effectiveness of the brains ahead! Intervention: 6 months results of a randomized controlled trial in school-aged children with mild traumatic brain injury. Journal of Head Trauma Rehabilitation 35(6): e490-e500	- Intervention Uni-modal psychoeducation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Jiang, C., Luo, Y., Qu, Y. et al. (2023) Pharmacological and Behavioral Interventions for Fatigue in Parkinson's Disease: A Meta-Analysis of Randomized Controlled Trials. Journal of Geriatric Psychiatry and Neurology 36(6): 487-495	- Intervention Systematic review with 12/13 studies investigating pharmacological interventions or uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 1/13 potentially relevant study, was checked against protocol criteria and was either not relevant or had been separately located by the literature search and screened.
Killington, M, Pearson, G, Campbell, E et al. (2021) Managing fatigue after an acquired brain injury: a pilot randomised controlled trial and qualitative investigation. International journal of therapy and rehabilitation 28(2): 1-14	- Intervention Uni-modal fatigue management intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Knowles, L.M., Hugos, C.L., Cameron, M.H. et al. (2022) Moderators of Improvements in Fatigue Impact After a Self-management Intervention in Multiple Sclerosis: A Secondary Analysis of a Randomized Controlled Trial. American journal of physical medicine & rehabilitation 101(4): 405-409	- Country Study conducted in the US.

Study	Reason for exclusion
Koopman, F.S., Voorn, E.L., Beelen, A. et al. (2016) No Reduction of Severe Fatigue in Patients with Postpolio Syndrome by Exercise Therapy or Cognitive Behavioral Therapy. Neurorehabilitation and Neural Repair 30(5): 402-410	- Intervention Uni-modal intervention (either CBT or exercise), not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Kos, D., Duportail, M., Meirte, J. et al. (2016) The effectiveness of a self-management occupational therapy intervention on activity performance in individuals with multiple sclerosis-related fatigue: a randomized-controlled trial. International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation 39(3): 255-262	- Intervention Uni-modal self-management intervention (energy conservation and goal setting for physical activity), but not multi-modal (combined physical and psychological) rehabilitation intervention for fatigue management.
Kratz, A.L., Atalla, M., Whibley, D. et al. (2020) Calling Out MS Fatigue: Feasibility and Preliminary Effects of a Pilot Randomized Telephone-Delivered Exercise Intervention for Multiple Sclerosis Fatigue. Journal of neurologic physical therapy : JNPT 44(1): 23-31	- Country Study conducted in the US.
Lau, S.C., Bhattacharjya, S., Fong, M.W. et al. (2022) Effectiveness of theory-based digital self-management interventions for improving depression, anxiety, fatigue and self-efficacy in people with neurological disorders: A systematic review and meta-analysis. Journal of telemedicine and telecare 28(8): 547-558	- Country Study conducted in the US.
Luo, F., Ye, M., Lv, T. et al. (2021) Efficacy of Cognitive Behavioral Therapy on Mood Disorders, Sleep, Fatigue, and Quality of Life in Parkinson's Disease: A Systematic Review and Meta-Analysis. Frontiers in Psychiatry 12: 793804	- Intervention Systematic review with 8/12 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 4/12 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Malysse, C., Romero-Galisteo, R.P., Merchan-Baeza, J.A. et al. (2021) Physical activity promotion programmes in childhood cancer patients and their impact on fatigue and pain: A systematic review. Children 8(12): 1119	- Population Systematic review including participants who are in protocol (1/6 study had people with CND) and out of protocol (2/6 studies had people with acute lymphoblastic leukaemia, 3/6 studies had people with an unspecified type of cancer). The study including participants with CND was checked against protocol criteria and was either not relevant or had been separately located by the literature search and screened.
Miller, P. and Soundy, A. (2017) The pharmacological and non-pharmacological interventions for the management of fatigue related multiple sclerosis. Journal of the Neurological Sciences 381: 41-54	- Intervention Umbrella review with 21/24 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 3/24 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Montanes-Masias, B., Bort-Roig, J., Pascual, J.C. et al. (2022) Online psychological	- Intervention

Study	Reason for exclusion
interventions to improve symptoms in multiple sclerosis: A systematic review. Acta Neurologica Scandinavica 146(5): 448-464	Systematic review with 8/13 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 5/13 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Moss-Morris, R., Harrison, A.M., Safari, R. et al. (2021) Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. Behaviour Research and Therapy 137: 103464	- Intervention Systematic review with 28/34 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management. The 6/34 potentially relevant studies, were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Norton, J., Joos, S., Cameron, M.H. et al. (2021) A multisite randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Very long term (5-6 year) follow-up at one site. Multiple Sclerosis Journal - Experimental, Translational and Clinical 7(4)	- Country Study conducted in the US.
Pilon, L., Frankenmolen, N.F., van der Zijp, J. et al. (2023) A short add-on sleep intervention in the rehabilitation of individuals with acquired brain injury: A randomized controlled trial. NeuroRehabilitation 53(3): 323-334	- Intervention Uni-modal energy conservation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Pilutti, L.A., Dlugonski, D., Sandroff, B.M. et al. (2014) Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. Multiple Sclerosis 20(5): 594-601	- Country Study conducted in the US.
Plow, M., Motl, R.W., Finlayson, M. et al. (2020) Intervention Mediators in a Randomized Controlled Trial to Increase Physical Activity and Fatigue Self-management Behaviors Among Adults With Multiple Sclerosis. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 54(3): 213-221	- Country Study conducted in the US.
Pottgen, J., Moss-Morris, R., Wendebourg, J.-M. et al. (2018) Randomised controlled trial of a self-guided online fatigue intervention in multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 89(9): 970-976	- Intervention Uni-modal energy conservation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Raina, K.D., Morse, J.Q., Chisholm, D. et al. (2016) Feasibility of a cognitive behavioral intervention to manage fatigue in individuals with traumatic brain injury: A pilot study. Journal of Head Trauma Rehabilitation 31(5): e41-e49	- Country Study conducted in the US.
Raina, K.D., Morse, J.Q., Chisholm, D. et al. (2022) An Internet-Based Self-Management Intervention to Reduce Fatigue Among People With Traumatic Brain Injury: A Pilot Randomized Controlled Trial. The American journal of occupational therapy : official publication of the	- Country Study conducted in the US.

Study	Reason for exclusion
American Occupational Therapy Association 76(4)	
Razazian, N., Kazeminia, M., Moayedi, H. et al. (2020) The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: A systematic review and meta-analysis. BMC Neurology 20(1): 93	- Intervention Systematic review with 31/31 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management.
Rooney, Scott, Moffat, Fiona, Wood, Les et al. (2019) Effectiveness of Fatigue Management Interventions in Reducing Severity and Impact of Fatigue in People with Progressive Multiple Sclerosis: A Systematic Review. International journal of MS care 21(1): 35-46	- Publication date Systematic review with 6/13 studies published 2013 or later, and 7/13 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Rooney, A.G., Hewins, W., Walker, A. et al. (2023) Lifestyle coaching is feasible in fatigued brain tumor patients: A phase I/feasibility, multicenter, mixed-methods randomized controlled trial. Neuro-Oncology Practice 10(3): 249-260	- Intervention Uni-modal energy conservation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Sajatovic, M., Ridgel, A.L., Walter, E.M. et al. (2017) A randomized trial of individual versus group-format exercise and self-management in individuals with Parkinson's disease and comorbid depression. Patient Preference and Adherence 11: 965-973	- Country Study conducted in the US.
Sangelaji, B., Smith, C.M., Paul, L. et al. (2016) The effectiveness of behaviour change interventions to increase physical activity participation in people with multiple sclerosis: a systematic review and meta-analysis. Clinical rehabilitation 30(6): 559-576	- Publication date Systematic review with 5/19 studies published 2013 or later, and 14/19 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Schuler, M.K., Hentschel, L., Kisel, W. et al. (2017) Impact of Different Exercise Programs on Severe Fatigue in Patients Undergoing Anticancer Treatment-A Randomized Controlled Trial. Journal of Pain and Symptom Management 53(1): 57-66	- Intervention Uni-modal physical exercise intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Sesel, A.-L.; Sharpe, L.; Naismith, S.L. (2018) Efficacy of Psychosocial Interventions for People with Multiple Sclerosis: A Meta-Analysis of Specific Treatment Effects. Psychotherapy and Psychosomatics 87(2): 105-111	- Reporting Studies included in the meta-analysis not reported.
Sgoifo, A., Bignamini, A., La Mantia, L. et al. (2017) Integrated Imaginative Distention Therapy to Cope with Fatigue. DIMMI SI Study: The First Randomized Controlled Trial in Multiple Sclerosis. Neurology and Therapy 6(2): 213-223	- Intervention Uni-modal imaginative distention therapy intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Siengsukon, C.F., Alshehri, M., Williams, C. et al. (2020) Feasibility and treatment effect of cognitive behavioral therapy for insomnia in individuals with multiple sclerosis: A pilot randomized controlled trial. Multiple Sclerosis and Related Disorders 40: 101958	- Country Study conducted in the US.

Study	Reason for exclusion
Siengsukon, CF; Beck, ES; Drerup, M (2021) Feasibility and Treatment Effect of a Web-Based Cognitive Behavioral Therapy for Insomnia Program in Individuals with Multiple Sclerosis: a Pilot Randomized Controlled Trial. International journal of MS care 23(3): 107-113	- Country Study conducted in the US.
Su, Y.; Yuki, M.; Otsuki, M. (2020) Non-pharmacological interventions for post-stroke fatigue: Systematic review and network meta-analysis. Journal of Clinical Medicine 9(3): 621	- Population Systematic review including participants out of protocol (adults with stroke). No studies checked against protocol criteria as did not include any participants with chronic neurological disorders included in protocol.
Sullivan, K.A., Blaine, H., Kaye, S.-A. et al. (2018) A Systematic Review of Psychological Interventions for Sleep and Fatigue after Mild Traumatic Brain Injury. Journal of Neurotrauma 35(2): 195-209	- Publication date Systematic review with 2/4 studies published 2013 or later, and 2/4 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
Thomas, P.W., Thomas, S., Kersten, P. et al. (2014) One year follow-up of a pragmatic multicentre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. BMC Neurology 14(1): 109	- Intervention Multi-modal intervention without exercise component (cognitive behavioural and energy effectiveness intervention), not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Thomas, S., Thomas, P.W., Kersten, P. et al. (2013) A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 84(10): 1092-1099	- Intervention Multi-modal intervention without exercise component (cognitive behavioural and energy effectiveness intervention), not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Titcomb, T.J., Sherwood, M., Ehlinger, M. et al. (2023) Evaluation of a web-based program for the adoption of wellness behaviors to self-manage fatigue and improve quality of life among people with multiple sclerosis: A randomized waitlist-control trial. Multiple Sclerosis and Related Disorders 77: 104858	- Country Study conducted in the US.
Torkhani, E, Dematte, E, Slawinski, J et al. (2021) Improving Health of People With Multiple Sclerosis From a Multicenter Randomized Controlled Study in Parallel Groups: Preliminary Results on the Efficacy of a Mindfulness Intervention and Intention Implementation Associated With a Physical Activity Program. Frontiers in psychology 12: 767784	- Outcomes Outcomes presented as pre- and post-intervention results in median and interquartile range. Data does not allow between group comparison of intervention and control groups and authors did not provide any statistical analysis of between group comparisons.
Turner, A.P., Hartoonian, N., Sloan, A.P. et al. (2016) Improving fatigue and depression in individuals with multiple sclerosis using telephone-administered physical activity counseling. Journal of Consulting and Clinical Psychology 84(4): 297-309	- Country Study conducted in the US.

Study	Reason for exclusion
Twisk, J.W.R., de Groot, V., Beckerman, H. et al. (2017) Cognitive behavioral therapy positively affects fatigue in patients with multiple sclerosis: Results of a randomized controlled trial. Multiple Sclerosis Journal 23(11): 1542-1553	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
van den Akker, L.E., Beckerman, H., Collette, E.H. et al. (2016) Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. Journal of Psychosomatic Research 90: 33-42	- Publication date Systematic review with 2/4 studies published 2013 or later, and 2/4 published pre-2013. Studies published 2013 or later were checked against protocol criteria and were either not relevant or had been separately located by the literature search and screened.
van der Linden, SD, Rutten, GM, Dirven, L et al. (2021) eHealth cognitive rehabilitation for brain tumor patients: results of a randomized controlled trial. Journal of neuro-oncology 154(3): 315-326	- Intervention Uni-modal cognitive/psychoeducation intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
van Kessel, K.; Wouldes, T.; Moss-Morris, R. (2016) A New Zealand pilot randomized controlled trial of a web-based interactive self-management programme (MSInvigor8) with and without email support for the treatment of multiple sclerosis fatigue. Clinical rehabilitation 30(5): 454-462	- Intervention Uni-modal internet delivered CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Veenhuizen, Y., Satink, T., Graff, M.J.L. et al. (2021) Mixed methods evaluation of a self-management group programme for patients with neuromuscular disease and chronic fatigue. BMJ Open 11(8): e048890	- Study design (adults) Non-randomised controlled trial in adults.
Voet, N., Bleijenberg, G., Hendriks, J. et al. (2014) Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT. Neurology 83(21): 1914-1922	- Intervention Uni-modal aerobic exercise or CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Voet, N.B.M. and Sasse, N. (2020) Cognitive behavioral therapy in FSHD. Neurologie und Rehabilitation 26(1): 23-31	- Publication type Narrative review, not a systematic review.
Voet, NBM, Bleijenberg, G, Hendriks, JCM et al. (2015) Both aerobic exercise and cognitive-behavioral therapy reduce fatigue in FSHD: an RCT. Nederlands tijdschrift voor geneeskunde 159(12)	- Intervention Uni-modal aerobic exercise or CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Walker, L.A.S.; Lindsay-Brown, A.P.; Berard, J.A. (2019) Cognitive Fatigability Interventions in Neurological Conditions: A Systematic Review. Neurology and Therapy 8(2): 251-271	- Intervention Systematic review with 2/2 studies investigating uni-modal interventions and not multi-modal rehabilitation interventions for fatigue management.
Wang, K., Li, K., Zhang, P. et al. (2021) Mind-Body Exercises for Non-motor Symptoms of Patients With Parkinson's Disease: A Systematic Review and Meta-Analysis. Frontiers in Aging Neuroscience 13: 770920	- Country Systematic review with 6/14 studies conducted in the US, 3/14 studies in China, 1/14 study in Korea, and 4/14 studies in Europe. European studies were checked against protocol criteria and were either not relevant or had been

Study	Reason for exclusion
	separately located by the literature search and screened.
Wendebourg, M.J., Heesen, C., Finlayson, M. et al. (2017) Patient education for people with multiple sclerosis-Associated fatigue: A systematic review. PLoS ONE 12(3): e0173025	- Publication date Systematic review with 1/10 studies published 2013 or later, and 9/10 published pre-2013. Study published 2013 or later was checked against protocol criteria and was either not relevant or had been separately located by the literature search and screened.
Xu, G.-Z., Li, Y.-F., Wang, M.-D. et al. (2017) Complementary and alternative interventions for fatigue management after traumatic brain injury: A systematic review. Therapeutic Advances in Neurological Disorders 10(5): 229-239	- Publication date Systematic review with 2/10 studies published 2013 or later, and 8/10 published pre-2013. Study published 2013 or later was checked against protocol criteria and was either not relevant or had been separately located by the literature search and screened.
Ymer, L., McKay, A., Wong, D. et al. (2021) Cognitive behavioural therapy versus health education for sleep disturbance and fatigue after acquired brain injury: A pilot randomised trial. Annals of Physical and Rehabilitation Medicine 64(5): 101560	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.
Ymer, L., McKay, A., Wong, D. et al. (2022) The design and evaluation of a health education control for comparison with cognitive behavioural therapy for individuals with acquired brain injury. Pilot and Feasibility Studies 8(1): 120	- Intervention Uni-modal CBT intervention, not multi-modal (combined physical and psychological) rehabilitation interventions for fatigue management.

CBT: cognitive behaviour therapy

Excluded economic studies

See Supplement 2 for the list of excluded studies across all reviews.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of multi modal (combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?

Research recommendation

What is the effectiveness and cost effectiveness of multi modal (i.e. combined physical and psychological) rehabilitation for fatigue management for children and young people with chronic neurological disorders?

Why this is important

Fatigue is a specific neurological symptom, which can be experienced by children and young people (CYP) with chronic neurological disorders (CND). For some, fatigue can be a significantly debilitating aspect of their condition which limits participation in life, education, and leisure. How fatigue is experienced differs across the CND conditions and is individual to the child or young person. Similarly, it is difficult to predict how children and young people with CND will respond to interventions to manage their fatigue. The adult evidence base suggests combinations of physical and psychological rehabilitation strategies may be helpful. There is currently little guidance on what type of fatigue intervention (or combination of interventions) would be most effective and cost effective in the management of fatigue in children and young people with CND.

Rationale for research recommendation

Table 10: Research recommendation rationale

Importance to 'patients' or the population	Little is known about the effectiveness of multimodal interventions which aim to manage fatigue in CYP with CND. Improving knowledge in this topic could help improve their fatigue management, and by extension, participation in day-to-day life and quality of life.
Relevance to NICE guidance	The use of multi modal fatigue interventions have been explored for adults, which highlighted a lack of evidence for CYP.
Relevance to the NHS	Reducing the impact of fatigue on CYP with CND could help improve their ability to participate (i.e., education, later employment, recreation and leisure activities, independence in ADLs). Additionally, given the potential differences in outcomes and intervention costs between various interventions, there may be differences in their cost effectiveness.
National priorities	High – the health and wellbeing of CYP is a key priority in the NHS Long Term Plan.
Current evidence base	This evidence review didn't include any studies in CYP with CND.
Equality considerations	CYP are unlikely to be currently receiving best care in their fatigue management (compared to adults).

ADL: activities of daily living; CND: chronic neurological disorders; CYP: children and young people

Modified PICO table

Table 11: Research recommendation modified PICO table

Population	Children and young people with rehabilitation needs due to the following chronic neurological disorders: • Acquired brain injury • Acquired spinal cord injury • Acquired peripheral nerve disorders • Progressive neurological diseases • Functional neurological disorders
Intervention	• Multi modal (combined physical and psychological) rehabilitation interventions for fatigue management
Comparator	Interventions compared with others in the same group or: • Placebo (placebo or sham) • Control (no intervention, waitlist, standard rehabilitation care alone, or 'usual care') • The same intervention (as listed under 'intervention') but varied in terms of: • Frequency ○ Intensity ○ Timing ○ Setting
Outcome	• Fatigue severity or impact on fatigue • Cost-effectiveness (including resource use measurements and QALY estimations using a validated preference-based measure such as the EQ-5D or SF-6D)
Study design	• Experimental study with random assignment to intervention and control groups • Experimental study with non-random assignment to intervention and control groups (quasi-randomised controlled trials, non-randomised controlled trials and prospective and retrospective cohort studies)
Timeframe	Long term
Additional information	None

EQ-5D: EuroQol 5-dimensions; SF-6D: short-form 6-dimension; QALY: quality-adjusted life years