SYSTEMATIC REVIEW

Diverse mechanisms and treatment strategies to confront fatigue in multiple sclerosis: A systematic review [version 1; peer review: 2 not approved]

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Abstract

Background: Firm conclusions about the applicability of treatment methods other than pharmacotherapy in treating fatigue in multiple sclerosis (MS) remain elusive. Our objective is to synthesize and review the epidemiological literature systematically and find an effective therapeutic plan for fatigue. The effect of individual treatment and combined treatment strategies are studied.

Methods: An electronic database search included EBSCO, PubMed, SCIENCE DIRECT and Scopus from January 1, 2013, to September 30, 2018. Search terms used are “Fatigue AND Multiple sclerosis AND therapy”. The articles included in the study are open access, published in last five years, not restricted to region and language. The search included randomized controlled trials (RCTs), observational studies, and systematic reviews.

Results: We included 13 systematic reviews, 10 RCTs and 7 observational studies. A Cochrane review on 3206 patients showed exercise therapy to have a positive effect on fatigue in RRMS patients. The EPOC trial showed switching interferon therapy or glatiramer to fingolimod showed improved fatigue levels. The FACETS trial showed incorporating behavioral therapy to ongoing recommended therapy is beneficial. Few observational studies demonstrated that fatigue is influenced by pain, mood problems, and depression.

Conclusions: The diverse pathology of fatigue related to MS is important in understanding and quantifying the role of each causal factor. Evidence reveals a positive effect on fatigue levels of RRMS patients with regular CBT and exercise-based combination therapy. Progressive forms of the disease have the worst prognosis. Individually aerobic exercises, behavioral therapy and pharmacotherapy have positive effects. A modified amalgamation of the same is a better hope for MS patients.

Keywords

Multiple sclerosis, fatigue, cognitive behavioral therapy, combined therapy, fatigue in MS.
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Author roles: Khadke S: Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Resources, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Siddique T: Methodology, Writing – Original Draft Preparation

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Introduction

“The idea that the brain can change its own structure and function through thought and activity is, I believe, the most important alteration in our view of the brain since we sketched out its basic anatomy and the workings of its basic component, the neuron.” – Norman Doidge.

Fatigue is a major symptom of multiple sclerosis (MS), which can lead to the difficulty in carrying out the daily errands and lowers the quality of life; it is prevalent in 80% of patients and hinders the quality of life in nearly 70%. Fatigue is disabling as it causes problems in daily life necessitating the need for a caregiver, causes embarrassment at workplaces where timebound work is, employment issues that can lead to premature retirement. Drugs used to treat MS are categorized as oral drugs, injectables, and infusions. Oral drugs include fingolimod, dimethyl fumarate, teriflunomide, and cladribine; injectables include IFNβ1a/1b, daclizumab, and glatiramer acetate; infusions include natalizumab, alemtuzumab, and ocrelizumab. Even upon arrival of new efficacious drugs which can halt the progression of the disease, fatigue remains the most troublesome symptom of patients, giving rise to forms of alternate treatment. This is a systematic review concerning how well pharmacological and non-pharmacological interventions influence fatigue levels in MS patients when compared to healthy adults.

MS is a chronic neurodegenerative disease characterized by disseminated plaque-like sclerotic lesions distributed in space and time. They are seen in both grey and white matter of CNS.

Figure 1. Global prevalence of MS in 2013. This shows that the disease has a high prevalence in cold countries especially The United States of America and Canada. ©MSIF 2013; reproduced with permission.
precursor cells comprise 5% of CNS cells; they express a proteoglycan called NG2 and can differentiate into mature oligodendrocyte. They also participate in immune reactions by responding to inflammatory cytokines hence limiting our strategy to promote the differentiation of precursor cells to mature oligodendrocytes. The genome-wide differences present in DNA methylation dictate the susceptibility of damage to oligodendrocytes. Neuroinflammatory mediators such as INF gamma, TNFα and ILβ promote synaptopathy, demyelination and axonal loss. This implies that if the inflammatory milieu is stopped, hence the subsequent progression of the disease.

There are four types of MS, relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and primary relapsing MS (PRMS). Initially, the disease starts as RRMS and then progresses to SPMS. The disease occurs most commonly in those aged 20–50 years. It occurs more commonly in females than in males, as seen in other autoimmune conditions. The prognosis of the disease depends on the age of presentation and number of exacerbations or relapses of the disease since the initial presentation. Actively demyelinating lesions in the background of inflammation causing blood-brain barrier dysfunction as seen in RRMS. Biomarkers of the disease include fetuin-A, nitric oxide synthase and osteopontin. Symptoms of MS include fatigue, visual problems, cognitive problem, dizziness, gait problem, sensory symptoms, sleep and sexual dysfunction.

The review describes fatigue treatment in MS using pharmacotherapy, exercise therapy and behavioral therapy in the last five years and their efficacy in treatment.

Methods
This review was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, using the methodology described in Cochrane Handbook for Systematic review of interventions.

Data sources and search
The following electronic databases were searched for articles published from the database on September 30, 2018: EBSCO, PubMed, SCIENCE DIRECT and Scopus databases were searched from January 1, 2013, to September 30, 2018. The search strategy included following words “Fatigue and Multiple sclerosis” OR “multiple sclerosis” OR “exercise in MS” OR “pharmacotherapy in MS” OR “Cognitive behavioural therapy and MS”.

Selection of studies
All abstracts identified by this search were independently screened by title and abstract by S.K and T.S. Duplicates were removed by screening based on title of the article and author name. All relevant full-text articles were evaluated for eligibility against the inclusion criteria. Any dispute which arose was solved by mutual consensus. As the scope of the article was limited to systematic review, additional analysis such as sub-group analysis and meta-regression was not done.

Data extraction
The data was extracted independently by two authors S.K and T.S. We collected data from the included randomized controlled trials (RCTs) regarding characteristics of patients, baseline data, exposed to quality analysis using AMSTAR grading shown in Table 1.

Inclusion/exclusion criteria
The articles included in the study are open access and not restricted by region or language. The selection included

| Table 1. Quality appraisal using AMSTAR guidelines. |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| STUDY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | SCORE | (On 11) |
| T. Yang et al. | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 8 |
| P. Miller and A soundly | No | Yes | Yes | No | Yes | Yes | No | No | No | No | 5 |
| M. Pearson et al. | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | 8 |
| L.E. van den Akker et al. | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 8 |
| A.E. Latimer-Cheung et al. | No | Yes | Yes | No | Yes | Yes | No | Yes | No | No | 5 |
| Fary Khan, Bhasker Amatya | UA | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | 6 |
| E. Taylor, R.E. Taylor-Piliae | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | 7 |
| Pagnini et al. | Yes | No | Yes | No | Yes | Yes | No | No | No | Yes | 4 |
| Phylo et al. | UA | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Heine M et al. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 10 |
| M. Asano, M.L. Finlayson | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| H. Cramer et al. | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Wendebourg et al. | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | 7 |
Randomized controlled trials, observational studies, and systematic reviews. We also included studies which has patients with clinically diagnosed MS and patients >18 years old with fatigue as their presenting complaint. We included studies which reported on patients with both primary and secondary MS. We excluded articles about neuropasticity in diseases other than MS. We excluded articles which focussed on non-motor aspects of MS or where experimental studies opinion articles, updates, Letters, study protocols, and extended abstracts. A list of excluded studies is available as Extended data.

**Risk of bias assessment**

Included studies were independently rated by S.K. and T.S. using the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. The rating process followed the description in the Cochrane Handbook for Systematic Review of Interventions (part 2:8.5.1) using RevMan version 5.1. Any disagreements during the process was solved by mutual discussions.

The quality of the identified studies was appraised using AMSTAR guidelines.

**Results**

**Studies identified**

We identified 1343 articles from the database search using Scopus, Science Direct, EBSCO and Pubmed with no additional articles from other sources. We found 1203 articles to be remaining after removal of duplicates. We excluded 1131 publications based on title and abstract and date of publication. We had 72 full-text articles assessed for eligibility of which 42 articles were excluded among which we excluded articles which related to cognitive changes. We included 10 RCT, 7 observational reviews and 13 systematic reviews for the study. A flow diagram is shown in Figure 2.

**Study characteristics**

The study characteristics and summary of systematic reviews is elaborated in Table 2. The study characteristics and summary of RCT is presented in Table 3. The study characteristics and summary of observational studies are depicted in Table 4.

**Results observed in systematic reviews and meta-analysis**

A Cochrane review showed exercise therapy to have a significant positive effect on fatigue in RRMS patients [standard mean deviation (SMD) -0.53, 95% confidence interval (CI) -0.73 to -0.33; P-value <0.01] but there was significant heterogeneity [I²=58%] among the trials compared. A few studies showed exercise improved walking speed with 10-minute walking test showing mean difference [MD] reduction in walking time of 1.76 s; [95% (CI), 2.47 to 1.06; P<0.001]. Another study comes in support of the use of exercise which shows that pooled Effect size was 0.57 (95%CI: 0.10–1.04, P = 0.02). These findings suggest that exercise can help to reduce fatigue in MS patients. A study by Taylor et al. mentions a study showing exercise worsening fatigue in MS (P<0.05).

Amantadine is anti-parkinsonian medication that gives an inconsistent improvement in 20–40% of patients over the short term. Yang et al. showed that amantadine might be the most effective drug for treating MS fatigue: SMD and CI were -1.09 [–1.30 to –0.87], and the z-score was 9.75 [P < 0.0001]; however, there was a high variation in number size of patients, causing heterogeneity to be 91%.

The two most effective drugs in treatment are natalizumab and alemtuzumab, but they cause progressive multifocal leukoencephalopathy (PML) due to John Cunningham virus and autoimmune diseases of thyroid along with thrombocytopenic purpura with immune glomerulonephritis respectively. A 6-month study in 2016, ECTRIMS showed no increase in mortality. Ocrelizumab, the first drug effective to slow down PPMS and which targets B cells in RRMS and PPMS, is in a phase 3 trial. A counter drug in SPMS is still to be discovered as IFNβ1b has not shown efficacy in American SPMS trials. Hence trials should be performed with combination therapy including ocrelizumab and IFNβ1b to counter SPMS, which has a poor prognosis.

Cognitive behavioural therapy (CBT) can help reducing fatigue in MS (pooled SMD = -0.71, 95% CI: -1.05 to -0.37, P = 0.77) as compared to active controls. Supporting studies also show a positive effect [SMD] = -0.47,95% CI] = -0.88; -0.06; I² = 73%]. A long-term positive effect of CBT [SMD = -0.30; CI -0.51; -0.08; I² = 0%] is also shown but had limited number of studies. Thus, CBT shows a positive effect on fatigue in MS. Practices like yoga show some effect compared to usual care [SMD = 20.52; 95% CI = 21.02 to 20.02; p = 0.04] but fail to prove better than exercise therapy [SMD = 0.03; 95% CI = 20.24 to 0.30; p = 0.83].

**Effect of interventions in RCTs**

Trials based on pharmacotherapy have shown that a change to new drugs like oral fingolimod was beneficial to many patients for fatigue in MS as shown by EPOC trial. The TSQM Global satisfaction scores were superior after the switch from intravenous disease-modifying therapy (DMT) to oral fingolimod [p<0.001]. Aerobic training exercises were delivered in ambulatory MS patient which showed improvements. This view was supported by the TREFAMS-AT trial (p<0.014). The non-fatigue related outcomes such anxiety, depression, and cognition showed improvement in the certain trials, which explains the dynamic connections with fatigue as a symptom.

Exercise therapy is a potential treatment modality, and when combined with education therapy it can cause behavior modification in many patients. This view was supported by the STEP IT UP and FACETS trial. It was able to prove that mobility was increased in intervention groups through the intervention time was relatively short (10 weeks).

The chronicity of symptoms in MS has a tremendous impact on the probability to show improvement to any therapy. It will be difficult to expect a positive change in a patient who has suffered chronic fatigue when compared to fatigue of new onset in...
MS patients. A study showed that multi-disciplinary rehabilitation on chronic fatigue patients was not effective in bringing the fatigue levels to a significant low that could be appreciated subjectively\textsuperscript{71,72}.

**Risk of bias analysis**

All criteria were judged as low, high or unclear risk of bias. In summary, most of the studies had a low risk of bias. The risk of bias graph is show in Figure 3 and Figure 4. Calkwood et al.\textsuperscript{67}, had high risk of bias as it lacks random sequence generation and allocation concealment. Calkwood et al.\textsuperscript{67}, Thomas et al.\textsuperscript{70}, failed to fulfil blinding of participants and outcomes in their respective studies, which were thus prone to performance and detection bias. It was unclear in a few studies whether allocation concealment and blinding of participants was carried out in studies like Heine et al.\textsuperscript{71} and Rietberg et al.\textsuperscript{72}.

As a result of heterogeneity among studies due to different study designs taken into consideration and a smaller number of participants in various studies owing to loss of follow up and the pathogenicity of the disease, a meta-analysis was not carried out.

**Discussion**

The primary outcomes in most of the trials used MSIS, FSS and CIS-20R scales\textsuperscript{69-71}. MSIS is a subjective scale based on a patient experiencing fatigue. CIS-20R subscale measures
<table>
<thead>
<tr>
<th>Study-place-year-design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparatives</th>
<th>Appraisal</th>
<th>Outcome</th>
<th>No. studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. Yang et al. China 2017</td>
<td>PwMS N=723 F=67.52%</td>
<td>Amantadine Vs n-acetyl carnitine Modafinil</td>
<td>Placebo</td>
<td>Jaded scale Cochrane risk of bias tool</td>
<td>Amantadine proved effective in treating fatigue in MS. L-carnitine was proposed to have similar effect as amantadine.</td>
<td>11 RCT from 5 databases</td>
</tr>
<tr>
<td>P. Miller and A Soundy UK 2017</td>
<td>PwMS N=17469 M-17.8% F-31.7% Rest not known</td>
<td>Amantadine Prokarin, Pemoline Carnitine, Modafinil Vs CBT mindfulness</td>
<td>Reviews including education (active control) No intervention (inactive control)</td>
<td>Amstar grading (Avg=6.5)</td>
<td>Modafinil proved to be beneficial. Pemoline and Carnitine did prove to be beneficial. Combination of physical and cognitive strategy proved beneficial.</td>
<td>24 Reviews with systematic quantitative RCT From 6 databases</td>
</tr>
<tr>
<td>Pearson et al. Australia 2015</td>
<td>PwMS N=655 M=169 F=463</td>
<td>aerobic endurance training, resistance training aquatics yoga</td>
<td>No exercise</td>
<td>Cochrane RoB tool</td>
<td>pwMS with exercise therapy had reduction in walking time in 10mWT of 1.76 sec. they also showed improvement in walking endurance(6m WT and 2m WT) (P&lt;0.001)</td>
<td>13 RCT From 8 databases</td>
</tr>
<tr>
<td>L.E. van den Akker et al. Netherlands 2016</td>
<td>PwMS N=520 M=100 F=420</td>
<td>CBT</td>
<td>Relaxation telephone delivered education and local care</td>
<td>Cochrane RoB tool</td>
<td>Overall CBT had positive short-term effect on fatigue. The long-term effect of CBT based treatment was described in 3 studies.</td>
<td>6 RCT 9 databases</td>
</tr>
<tr>
<td>A.E. Latimer-Cheung et al. Canada 2013</td>
<td>PwMS N=1338*</td>
<td>Aerobic training, resistance training, combined both.</td>
<td>No intervention</td>
<td>PEDro score for RCT Downs and Black scale for non RCT</td>
<td>Exercise done twice a week with moderate intensity increases aerobic capacity with muscle power. It may enhance mobility, fatigue, and health-related QoL.</td>
<td>23 RTC 31 NON-RTC 7databases</td>
</tr>
<tr>
<td>Fary Khan, Bhasker Amatya Australia 2017</td>
<td>PwMS N=16602*</td>
<td>Multiple interventions</td>
<td>No intervention</td>
<td>AMSTAR</td>
<td>Physical therapy for enhanced activity and participation while educational programs reduced fatigue (strong evidence). Multidisciplinary rehabilitation had moderate evidence. Limited for psychological and symptom management programs (fatigue, spasticity).</td>
<td>15 Cochrane review 24 OTHER REVIEW 5 databases</td>
</tr>
<tr>
<td>E. Taylor, R.E. Taylor-Piliae USA 2017</td>
<td>PwM N=193*</td>
<td>Tai chi</td>
<td>Tai chi group vs non-tai chi or control group</td>
<td>An established tool with 16 study elements</td>
<td>One study proved enhanced cognition and psychosocial fatigue scores (p &lt;0.05). One study reported worsening of fatigue in controls (p &lt; 0.05).Rest revealed no significance</td>
<td>3 RCT 5 Quasi-experimental studies 13 databases</td>
</tr>
<tr>
<td>Study-place-year-design</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparatives</td>
<td>Appraisal</td>
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<tr>
<td>Pagnini et al. Italy 2014</td>
<td>PwMS N= 5705*</td>
<td>CBT and other psychological treatments</td>
<td>Usual care</td>
<td>QUOROM statements</td>
<td>Fatigue improved following relaxation training, meditation, stress management, and coping.</td>
<td>22 RCT</td>
</tr>
<tr>
<td>Phylo et al. Australia 2018</td>
<td>PwMS N= 1249*</td>
<td>Psychological interventions CBT</td>
<td>comparators were non-active/active controls (relaxation or psychotherapy)</td>
<td>EPHPP Hamilton Tool</td>
<td>1. CBT decreased levels of fatigue w.r.t non-active controls (P= 0.07) and with active controls (P = 0.77). 2. Relaxation (P = 0.37) and mindfulness interventions (P= 0.59) decreased fatigue levels compared to non-active control</td>
<td>20 14 RCT 6-others From 4 databases</td>
</tr>
<tr>
<td>Heine M et al. Netherlands 2015</td>
<td>PwMS N= 3206*</td>
<td>Exercise therapy alone vs endurance training vs mixed training vs others</td>
<td>No exercise group two exercise therapies</td>
<td>Cochrane RoB tool</td>
<td>1. Exercise therapy improved fatigue levels (P &lt; 0.01) and so the others 2. Endurance exercise (P &lt; 0.01) 3. Mixed exercise (P &lt; 0.01) 4. Other exercise (P &lt; 0.01)</td>
<td>72 RCT</td>
</tr>
<tr>
<td>Asano, Finlayson Canada 2014</td>
<td>PwMS N= 1499*</td>
<td>Pharmacological Exercise Education</td>
<td>Non-pharmacologic Non-exercise Non-education</td>
<td>Cochrane RoB tool</td>
<td>Rehabilitation- exercise and education have a strong effect in decreasing the impact or severity of fatigue compared to the fatigue medications prescribed very often like Amantadine and Modafinil. Rehabilitation could be the initial treatment of choice contrary to ongoing standards.</td>
<td>25 RCT</td>
</tr>
<tr>
<td>Holger Cramer et al. Germany 2014</td>
<td>PwMS N= 670*</td>
<td>Yoga</td>
<td>Usual care, exercise non-pharmacological</td>
<td>Cochrane RoB tool</td>
<td>1. Yoga had short term effect on fatigue (p = 0.04) 2. No evidence found yoga to be better than exercise (p = 0.83)</td>
<td>7RCT</td>
</tr>
<tr>
<td>Wendebourg et al. Germany 2017</td>
<td>PwMS N=1021*</td>
<td>CBT</td>
<td>Non-CBT approaches(education)</td>
<td>Cochrane RoB tool</td>
<td>CBT based treatment approach has a positive effect on fatigue levels. a need for multidimensional treatment emphasized.</td>
<td>10 RCT</td>
</tr>
</tbody>
</table>

EPHPP, Effective Public Health Practice Project; Cochrane RoB tool, Cochrane risk of bias tool.
<table>
<thead>
<tr>
<th>First author</th>
<th>Crossover design?</th>
<th>Randomized/analyzed (n)</th>
<th>Duration of disease IN YEARS (SD)</th>
<th>EDSS scores, median IQR(SD)</th>
<th>Duration of treatment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susan Coote</td>
<td>No; 92/65</td>
<td></td>
<td>6.85 (5.9)</td>
<td>3.3(0.7)</td>
<td>36 weeks</td>
<td>Both groups showed improvements in post-intervention fatigue levels in PwMS at the end of 36 weeks. This showed a positive effect of behavioral therapy with exercise.</td>
</tr>
<tr>
<td>Sara Hayes</td>
<td>No; 92/65</td>
<td></td>
<td>6.85 (5.9)</td>
<td>3.3(0.7)</td>
<td>36 weeks</td>
<td>ITT analysis showed no difference between the two groups of study. A secondary analysis showed a significant treatment effect favoring the intervention group (p=0.04).</td>
</tr>
<tr>
<td>Martin Heine</td>
<td>No; 89/89</td>
<td></td>
<td>6.85 (5.9)</td>
<td>3.0 (0.2–15.3)</td>
<td>16 weeks</td>
<td>A short-lived post-intervention effect was seen which did not sustain in follow up period.</td>
</tr>
<tr>
<td>Jonathan Calkwood</td>
<td>No; 1053/1053</td>
<td></td>
<td>4.44 to 4.57</td>
<td>12.5 (13.3)</td>
<td>6 months</td>
<td>A change to fingolimod from GA, IM IFN beta-1a, SC IFN beta-1a showed significant changes in TSMQ global satisfaction scores. In those who switched to fingolimod from SC IFN beta-1a, remarkable reduction in fatigue was seen, except those remaining on GA and in IFN beta-1a.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of eligible participants</th>
<th>Treatment groups (n)</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years at baseline, mean (SD)</td>
<td>Exercise + social cognitive therapy (SCT) (33) vs exercise + education (32)</td>
<td>Both groups showed improvements in post-intervention fatigue levels in PwMS at the end of 36 weeks. This showed a positive effect of behavioral therapy with exercise.</td>
</tr>
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<td>A short-lived post-intervention effect was seen which did not sustain in follow up period.</td>
<td></td>
</tr>
<tr>
<td>Aerobic exercise (35) vs consultation with MS nurse (46)</td>
<td>1. Physician-confirmed MS cases 2. EDSS score of 0-3 3. Sedentary lifestyle</td>
<td>Both groups showed improvements in post-intervention fatigue levels in PwMS at the end of 36 weeks. This showed a positive effect of behavioral therapy with exercise.</td>
</tr>
<tr>
<td>GA to fingolimod (n=262)</td>
<td>Remaining on GA (n=74)</td>
<td>1. Physician-confirmed MS cases 2. EDSS score of 0-3 3. Sedentary lifestyle</td>
</tr>
<tr>
<td>IM IFN beta-1a to fingolimod (n=205)</td>
<td>Continuing IM IFN beta-1a (n=48)</td>
<td>1. Physician-confirmed MS cases 2. EDSS score of 0-3 3. Sedentary lifestyle</td>
</tr>
<tr>
<td>SC IFN beta-1a to fingolimod (n=196)</td>
<td>Continuing SC IFN beta-1a (n=58)</td>
<td>1. Physician-confirmed MS cases 2. EDSS score of 0-3 3. Sedentary lifestyle</td>
</tr>
<tr>
<td>IFN beta-1b to fingolimod (n=125)</td>
<td>Continuing IFN beta-1b (n=139)</td>
<td>1. Physician-confirmed MS cases 2. EDSS score of 0-3 3. Sedentary lifestyle</td>
</tr>
</tbody>
</table>

**Table 3. Summary of included randomized controlled trials.**
<table>
<thead>
<tr>
<th>First author</th>
<th>Crossover design?</th>
<th>Randomized/analyzed (n)</th>
<th>Characteristics of eligible participants</th>
<th>Treatment groups (n)</th>
<th>Duration of disease in YEARS (SD)</th>
<th>Duration of treatment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ari J Green</td>
<td>Yes; 50/50</td>
<td>40.1(10.3)</td>
<td>1. Stable RRMS patients ≤15 years of disease duration 2. Patients had a demyelinating injury in the visual pathway 3. Patients had no significant difference was found between the two groups (including fatigue) except peak expiratory flow (p = 0.01)</td>
<td>Group 1 received 90-day clemastine fumarate followed by 60-day placebo; Group 2 received 90-day placebo followed by 60-day clemastine fumarate.</td>
<td>1.5 (1.1)</td>
<td>150 days</td>
<td>Greater improvement in latency in group 2 than in group 1. Both groups showed improved fatigue levels.</td>
</tr>
<tr>
<td>Arno Kerling</td>
<td>No; 60/60</td>
<td>45.6 ± 9.0 (EWG) with a mean of 43.9(10.2)</td>
<td>1. Maximum value of 6 on EDSS. 2. Adult age (18–65 years). 3. Clinical neurologist-confirmed cases</td>
<td>Combined work out group (30) Vs Endurance work out group (30)</td>
<td>2.8 (1.2)</td>
<td>3 months</td>
<td>Combination of aerobic training and exercise had improvement in aerobic capacity and peak expiratory flow. Both groups showed improvement.</td>
</tr>
<tr>
<td>Alexander Tallner</td>
<td>No; 126/108</td>
<td>40.8 (9.3)</td>
<td>1. EDSS score of less than or equal to 4.0 2. At least 4 weeks of clinical stability</td>
<td>Internet based e-training (59) vs wait list control (67)</td>
<td>3.0 (2.5)</td>
<td>6 months</td>
<td>No significant difference was found between the two groups (including fatigue) except peak expiratory flow (p = 0.01)</td>
</tr>
<tr>
<td>Fred D. Lublin</td>
<td>No; 16/16</td>
<td>48.0 (36–58)</td>
<td>1. Age between 18 and 65 years (both RRMS and SPMS) 2. Disease duration of at least 2 years 3. Evidence of active disease on MRI or cerebrospinal fluid analysis 4. Cardiac, pulmonary, renal and pulmonary function should be normal</td>
<td>1 unit of PDA-0001(6) vs 4 units of PDA-0001(6) vs placebo (4)</td>
<td>4.8 (1.5 – 6.5)</td>
<td>6 months</td>
<td>It was found safe to infuse mesenchymal like cells to patients with MS. No increments in EDSS score more than 0.5. No worsening of MS noted.</td>
</tr>
<tr>
<td>Marc B. Rietberg</td>
<td>No; 48/44</td>
<td>46(9.25)</td>
<td>1. ≥18 years, ambulatory. 2. Clinically diagnosed MS 3. Should have chronic fatigue fulfilling the MSCCPG definition</td>
<td>Multidisciplinary Rehabilitation (25) vs nurse consultations (25)</td>
<td>3.5 (2.5)</td>
<td>24 weeks</td>
<td>Within-group effects were found to be significant for both primary (0.05≤p&lt;0.01) and secondary (0.1≤p&lt;0.01) outcome measures from baseline to 12 months (P = 0.39) or 24 weeks (P = 0.14)</td>
</tr>
<tr>
<td>First author</td>
<td>Crossover design?</td>
<td>Age in years at baseline, mean (SD)</td>
<td>Characteristics of eligible participants</td>
<td>Treatment groups (n)</td>
<td>EDSS scores, median IQR(SD)</td>
<td>Duration of disease IN YEARS (SD)</td>
<td>Duration of treatment</td>
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<tr>
<td>S. Thomas</td>
<td>No; 164/131</td>
<td>49.05(9.65)</td>
<td>1. Clinically diagnosed MS.</td>
<td>FACETS plus CLP (84) vs CLP (80)</td>
<td>Not available</td>
<td>Different duration from &lt; 1 year to &gt; 16 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Peter W Thomas</td>
<td>No; 164/131</td>
<td>49.05(9.65)</td>
<td>1. Clinically proven MS diagnosis with FSS SCORE &gt; 4</td>
<td>FACETS plus CLP (84) vs CLP (80)</td>
<td>Not available</td>
<td>Different duration from &lt; 1 year to &gt; 16 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Vanessa Vermöhlen</td>
<td>No; 70/67</td>
<td>51 (46–55)</td>
<td>1. MS patients older than 18 years</td>
<td>Hippotherapy plus standard care (32) vs standard care alone (38)</td>
<td>5.4 (0.9) (at inclusion) 21 (31%) = ≤5 46 (69%) = ≤5</td>
<td>17.3 (11–23)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Author and year</td>
<td>Number of patients (control/experimental)</td>
<td>Mean ± SD</td>
<td>Characteristics of eligible participants</td>
<td>Duration of treatment and treatment given</td>
<td>Duration of disease in control and experiment</td>
<td>EDSS scores ± SD</td>
<td>Results</td>
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<tr>
<td>Adamczyk-Sowa et al.</td>
<td>n = 122 (20/102)</td>
<td>10 ± 11.6 (for controls) 86 ± 10.28 (for RRMS pretreated group), 42 ± 10.06 (RRMS INF-beta), 15 ± 7.01 (SP/PP MS Mitoxantrone) (41.90 ± 7.13 RRMS Relapse)</td>
<td>All PwMS diagnosed, according to the McDonald criteria. Melatonin</td>
<td>90 days melatonin</td>
<td>Control = NA, Pretreated = 1.85 ± 1.21, RRMS INFβ = 6.27 ± 2, RRMS Mitoxantrone = 20.88 ± 13.65 RRMS Relapse = 6.54 ± 5.13</td>
<td>Control = 0, RRMS Pretreated = 1.85 ± 0.95, RRMS INFβ = 2.92 ± 1.24, RRMS Mitoxantrone = 5.68 ± 1.51, RRMS Relapse = 3.96 ± 1.98</td>
<td>LHP (lipid hydroxy peroxides) and homocysteine concentration was higher in all studied MS groups vs. controls which decreased after melatonin usage. In the RRMS-relapse group levels of homocysteine were significantly higher compared to the RRMS-pre-treated group. The fatigue score was significantly lower in RRMS pre-treated group compared to RRMS-INF-beta and PP/SP MS-mitoxantrone treated patients.</td>
</tr>
<tr>
<td>Aydin, T et al.</td>
<td>n = 40</td>
<td>32.83 ± 3.64</td>
<td>1. acute exacerbation of MS symptoms. 2. An Ashworth spasticity score over 2 3. EDSS score over 4.</td>
<td>12 weeks of Calisthenic exercises</td>
<td>6.97 ± 3.15</td>
<td>&lt; 4.5, Hospital based group = 3.6 ± 1.3, Home based group = 3.4 ± 2.1</td>
<td>Significant improvements in terms of the BBS, HADS-A and Musi-QoL scores after 12 weeks of home and hospital-based exercises. The HADS-D score improved on the in hospital-based patients only. No significant difference in the FSS score (p &lt; 0.05).</td>
</tr>
<tr>
<td>Baert, I et al.</td>
<td>n = 290 PwMS, 284 completed</td>
<td>49.7 ± 10.8</td>
<td>Included subjects had a definite diagnosis of MS, EDSS score ≤ 6.5</td>
<td>Single time experiment performed Physical rehabilitation exercises</td>
<td>11.9 ± 8.1</td>
<td>4.8 ± 1.5</td>
<td>Moderate to severely disabled pwMS performed well on MSWS-12, 2MWT, and 6MWT but not on 25MF WT. (MWT - minute walking test)</td>
</tr>
<tr>
<td>Burschka, J. M. et al.</td>
<td>n = 32 PwMS, 15</td>
<td>TAU = 43.6 ± 8.0 Tai Chi = 42.6 ± 9.4</td>
<td>1. MS patients (any type) 2. EDSS &lt; 5 3. Relapse free for a month prior study</td>
<td>6 months Tai chi</td>
<td>TAU* = 7.8 ± (6.8) Tai Chi = 6.0 ± (4.7)</td>
<td>&lt; 5</td>
<td>Balance, coordination and life satisfaction had improved with Tai Chi treatment comparing to TAU. Fatigue and depression were found decreased with Tai Chi treatment.</td>
</tr>
<tr>
<td>Author number of patients (control/experimental)</td>
<td>Age Of participants Mean ± SD</td>
<td>Characteristics of eligible participants intervention/ treatment</td>
<td>duration of treatment and treatment given</td>
<td>Duration of disease in control and experiment</td>
<td>EDSS scores± SD</td>
<td>Results</td>
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<td>Collett, J et al.(1) n = 23, PwMS=14, Control=9</td>
<td>MS= 52.4 ±8.1, Control= 49.6 ±8.6</td>
<td>1) Clinically definite MS, (2) Be the age of 18 years (3) have the adequate mental capacity to consent, (4) Clinically stable (5) Able to use a cycle ergometer.</td>
<td>Single time exercise test performed Multiple intensity exercises</td>
<td>14.1 SD 9.7</td>
<td>Not Provided</td>
<td>-Controls proved better on the exercise test (p &lt; 0.05). -PwMS took longer to recover as the intensity of exercise increased (45% at 6 min; 60% at 15 min; 90% at 35 min) and correlating with Tympanic temperature. MEParea was significantly depressed in both groups at 45% and 60% (p &lt; 0.001), in the MS group which correlated well to recovery time measured by RPE. RPE= Borg’s ratings of perceived exertion. MEP= motor evoked potential</td>
<td></td>
</tr>
<tr>
<td>Fernandez-Munoz, J. J. et al.(2) n= 108 PwMS</td>
<td>44 ± 8</td>
<td>Definite MS according to the modified McDonald criteria.</td>
<td>NA</td>
<td>12.5±8.0</td>
<td>3.4±1.7</td>
<td>Fatigue score was associated with bodily pain (P&lt;0.01), physical function (P&lt;0.01) and mental health (P&lt;0.01), and with positive association with depression (P&lt;0.01). Depression had negative association with bodily pain (P&lt;0.01) and mental health (P&lt;0.01) Greater the body pain, greater were levels of depression.</td>
<td></td>
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<tr>
<td>Soysal Tomruk, M. et al.(3) n = 11 PwMS, 12 Control</td>
<td>Median values mentioned in the study MS=52 (35–66) control=50 (38–65)</td>
<td>Age :18 to 65 years, 2≥EDSS score ≤5.</td>
<td>Ten-week</td>
<td>-</td>
<td>3.5 (2.0–5.0)</td>
<td>Postural control and fatigue levels were significantly worse in PwMS w.r.t healthy controls (p&lt;0.05) but improved sensory interactions were noted (p&lt;0.05) and no effect on postural control (p&gt;0.05).</td>
<td></td>
</tr>
</tbody>
</table>

TAU, treatment as usual.
Figure 3. Risk of bias graph.

Figure 4. Risk of bias summary.
References


fatigue severity. FSS measures the impact of fatigue on normal functioning. The changes measured on any scale should be accompanied by a change in FSS scale to make it clinically meaningful to adopt as a standard measure for generalizability. Not every severely fatigued patient (in most cases of advanced MS) will give expected results on standard exercising protocol. It is an arguable viewpoint leading to reverse causality whether exercise therapy is worsening fatigue levels in MS patients as supported by a systematic review by Taylor et al.17.

Considering the therapeutic interventions for MS-related fatigue, a variety of exercise methods (pilates, calisthenics, Tai Chi and aerobic) of exercises have gained attention. Numerous studies have shed light on the efficiency of exercise for the PwMS, almost all studies designated the exercise as a remarkable factor in improving the fatigue and its related distress in MS. Certain observational studies have been conducted to find out if the cause of fatigue in PwMS is the physical activity instead of neural demyelination and lack of neuroplasticity. One cross-sectional study ruled out the possibility of fatigue associated with the physical activity instead they found a strong association between the mental health and fatigue18.

Fatigue in MS can be due to depression, which intercedes the association between neuronal issues and physical conditions44. Pharmaceutical interventions like melatonin supplementation have been effective to treat the fatigue related to MS45. Melatonin can act as anti-inflammatory and immunomodulatory drug that does not cross the blood-brain barrier. The anti-oxidative effect can be used to treat MS patients as they have high oxidative stress owing to elevated levels of plasma lipid peroxide and activated nitrosative-oxidative pathways46.

An observational retrospective study showed that switching from interferon-β to glatiramer improved work productivity, activity impairment and health-related quality of life [HRQoL] and fatigue. Transcranial magnetic stimulation [TMS] is an innovative way to record neurophysiological responses by measuring corticospinal-neuromuscular pathway excitability. The persistent excitation of brain neurons plays an important role in progressive forms of the disease83.

Plasticity is a functional reorganization of neurons carried out through anatomical reorganization and axonal sprouting with synaptogenesis. Physical training is known to induce compensatory plasticity and increases activity-dependent synaptic potentiation. Exercise is known to cause an increase in endocannabinoid signalling86.

The summary of included observational studies can be found in Table 4.

Conclusion

The diversity of pathological phenomena involved in fatigue related to MS is a major concern in understanding and quantifying the role of each causal factor. Our study has found a significant positive effect on fatigue levels of RRMS patients with regular CBT and exercise-based combination therapy. These results were not supported in case of PPMS or SPMS patients due to the aggressive nature of the disease. Emphasizing the clinical significance of combinational therapy which can be prescribed in MS, yet this does not undermine the need for statistical analysis and correlation. Future research should focus on improving the quality of life of progressive forms of MS. Factors responsible for a high drop-out rate should be studied and correlated with morbidity and mortality rates. We believe an amalgamation of sound mental health, physical health, and pharmacological health shall tone down or blunt the effect of fatigue in the daily life of MS patients.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Open Science Framework: DIVERSE MECHANISMS AND TREATMENT STRATEGIES TO CONFRONT FATIGUE IN MULTIPLE SCLEROSIS -A SYSTEMATIC REVIEW. https://doi.org/10.17605/OSF.IO/W5DA4

This project contains references for all excluded studies.

Extended data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Reporting guidelines


Grant information

The author(s) declared that no grants were involved in supporting this work.

Page 15 of 22
Open Peer Review

Current Peer Review Status: 

Version 1

Reviewer Report 18 June 2019

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Tomas Kalincik
CORe, Department of Medicine, University of Melbourne, Melbourne, Vic, Australia

This article aims at providing a systematic review of literature on the treatment of fatigue in multiple sclerosis. This is an important topic, as management of MS-related fatigue is a difficult subject and the results achieved in clinical practice are often frustrating to clinicians and patients alike. Unfortunately, the review falls short of its goal, providing only a superficial summary of the identified literature and a discussion based on a handful of selected anecdotes. The review would benefit from a more systematic approach to the topic.

Major comments:
The systematic review only included open access articles. This is potentially a significant limitation. How may otherwise eligible articles were excluded on these grounds?
The information summarised in the Introduction is selective and only remotely related to this article. The referencing style in the Introduction is suboptimal, with only limited number of indirect references cited.
The summary given in the Introduction, paragraph 5 is unnecessary. Most of this information is not immediately relevant to this manuscript and the section is not appropriately referenced. Similarly, the information shown in paragraph 6 is patchy and poorly referenced.
The authors cite the old phenotypic classification of MS. Instead, the 2013 revisions of the classification of MS phenotypes (Lublin et al., Neurology 2014[Ref-1]) should be used.

During screening, the authors have excluded a large number of identified articles. This does not impact negatively on the quality of the systematic review but it highlights that the search terms employed were very broad.

The Results are hard to follow. The effect of different interventions on physical performance and fatigue are presented intermittently. In fact, the most of the section on the results of meta-analyses focuses on the effects of treatments on physical performance, with only a very brief mention of the reported effect on fatigue. The references of the individual results are scattered and often given without the appropriate context (for instance “6-month study in 2016, ECTRIMS showed no increase in mortality.”) The summary of the safety issues mentioned for some of the presented interventions is not balanced. The authors erroneously state that there is no evidence of therapeutic effect in SPMS, whereas siponimod has in fact
shown effect on slowing progression of disability in a phase 3 trial (EXPAND).
There is some duplication of the reported results, as some of the clinical trials were also included in the
meta-analyses. This is unavoidable, but the amount of overlap between the meta-analyses and the trials
reported individually in this review should be reported.
An improvement in 20-40% of patients treated with amantadine is referenced – it is unclear which domain
and in what test this improvement involves. Similarly, it is unclear what is meant by the statement ’The two
most effective drugs in treatment are natalizumab and alemtuzumab…’.
Does this relate to their effect on relapses/disability/MRI or fatigue?
The results of the individual randomised controlled trials should be summarised not only with p values but,
most importantly, with the measures of effect size (both point and interval estimates).
The authors mention an issue of the efficacy of interventions in the context of the duration of the
symptoms. This should be expanded upon and provided with more supporting evidence if this theme is to
be retained within the article.

The manuscript would benefit from a stylistic review (a few examples – Introduction, paragraph 2, lines
6-7; Introduction, paragraph 3, lines 12-16; Introduction, paragraph 5, last line; Introduction, paragraph 5,
lines 10-12; Methods, Inclusion/Exclusion criteria, lines 9-11; Figure 2 etc.). The authors should also use
terminology more accurately – e.g. ’widespread MS investigation’, ’disease burden’, ’experimental
studies’. The formulation “MS is affecting 2,000,000 people worldwide and 400,000 people in the United
States per year” implies that the cited information represents incidence, whereas the numbers given are
keeping with MS prevalence.
The Discussion is not systematically structured and would benefit from more thorough, systematic
evaluation of the mentioned topics. These include the present anecdotes related to the link between
depression and fatigue, use of melatonin, TMS and plasticity. An in-depth discussion of the summarised
literature, including critical appraisal of the presented studies and meta-analyses, is needed.

The opening statement of the Discussion provides a perspective on relevant measurable outcomes in the
tests of MS-related fatigue. This discussion should be linked to the results presented and the magnitude
of the impact of the studied interventions on FSS should be evaluated.

The authors have phrased the conclusion in the fashion of an original study (“Our study has found a
significant positive effect…”). However, it should be remembered that this article is a systematic review of
literature, in which no novel results were generated. The Conclusion section should use the language of a
review. In this context, references to ’significant’ findings are not appropriate.

The following proposed conclusions are not supported by the results of the reported trials, including the
following:
- The suggestion that CBT and exercise-based therapies are not associated with better control of
  fatigue due to a more aggressive nature of PPMS and SPMS relative to RRMS
- The proposed need for combination therapy for MS, which is also being implied as an accessible
  option (please note that combination immunotherapy is not approved for use in MS)

The sentence containing “…should focus on improving the quality of life of progressive forms of MS”
objectifies patients and should be rephrased.

Minor comments:
Table 1: should provide explanation of the AMSTAR items in a footnote.
Table 2: Minor inconsistencies are present (such as n-acetyl carnitine vs. L-carnitine; the format of
presenting control groups)
References

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
No

*Competing Interests:* Tomas Kalincik served on scientific advisory boards for Roche, Sanofi-Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi-Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanofi, Teva, BioCSL and Merck and received research support from Biogen. None of these disclosures is directly relevant to the presented article or its topic.

*Reviewer Expertise:* multiple sclerosis, neuroimmunology, biostatistics, clinical outcomes research

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 20 May 2019
https://doi.org/10.5256/f1000research.19959.r48607

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Andrew Soundy
School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

Overall, I think more time is needed to explain what you did and show the reader that a quality process has been undertaken. Some points below are critical for me.

Abstract
As a reader I am not sure how you integrated and weighted findings from different designs e.g., you
mention two random trials in the results EPOC and FACETS – yet review evidence would include more accurate results and you have identified 13 reviews?

Introduction
Does the reader need to know about the different drugs for treatments of MS or the main point which is fatigue remains
Not sure of the need for Figure – given the focus and aim of this work

There is no overview of why a review or what type of review is needed within this section?

Methods
There is no protocol
If you are using Cochrane then you would include systematic reviews in your synthesis – you would ideally aim to get a meta-analysis done of past empirical research. So the design is questionable. As your review is mixed methods review requiring aspects which are needed for mixed methods design including a decision around the point of integration of data.
If you used Cochrane as a basis your key words would have likely increased and the number of databases and search methods would be different from what you state
Your methods has no detail on synthesis as point in abstract is made

Results
Page 5 Think about the how you lay out the information – currently for me there is limited information which is hard to understand how and why you have presented it like this.
Think about how you integrate the quality assessment onto findings

Discussion
Without clarity from above – I can't assess the discussion currently

Are the rationale for, and objectives of, the Systematic Review clearly stated?
No

Are sufficient details of the methods and analysis provided to allow replication by others?
No

Is the statistical analysis and its interpretation appropriate?
No

Are the conclusions drawn adequately supported by the results presented in the review?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Methodology and publications in this area including one cited by the authors.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.
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