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Miller, Philippa; Soundy, Andrew

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The Pharmacological and Non-Pharmacological Interventions for the Management of Multiple Sclerosis Related Fatigue~~The Pharmacological and Non-Pharmacological Interventions for the Management of Fatigue Related Multiple Sclerosis~~

Miller, N. Philippa. MSc-University of Birmingham. Email: pnmiller93@outlook.com-07989835288

Soundy, A. PhD. University of Birmingham. Email: a.a.soundy@bham.ac.uk- +44 (0)121 414 8385

University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

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Authors:

Philippa Miller:

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Author: Drafting the manuscript for content, Acquisition of data, Study concept and Analysis of data

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Andy Soundy:

Author: Acquisition of data, critical revision of the manuscript for important intellectual content. Corresponding author, study supervision and final approval of the version to be submitted for review.

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Abstract

Title: Pharmacological and Non-Pharmacological Interventions for the Management of Fatigue Related Multiple Sclerosis: A Review of Reviews

Aim: The clinical aim was to provide up-to-date evidence-based recommendations for the treatment of MS-related fatigue (MSRF). The scientific aim was to prioritize topics for future randomized clinical trials with sufficient power. ~~The clinical aim: to provide up-to-date evidence-based recommendations for the treatment of MS-related fatigue; and the scientific aim: …to prioritize topics for future randomized clinical trials with sufficient power.~~

Methods: A systematic search of review based research that considered MSRF in adults (18 years and over) was undertaken in May 2016. Data from reviews was extracted, critically appraised and synthesised using four specific techniques.

Results: A total of 24 reviews were identified (17 non-pharmacological, 5 pharmacological, 2 combining both), which contained 339 studies on interventions deigned to improve MSRF. The methodological quality of the reviews was identified by an average AMSTAR score of 6.5 (SD=1.87: 95% CI=5.75-7.25).

No pharmacological intervention had strong evidence for improving MSRF. Limited/ conflicting evidence was found for Amantadine and Prokarin and potential benefits for Modafinil were identified. Pemoline and Carnitine contained unclear/no evidence for fatigue management.

Non-pharmacological interventions produced mixed conclusions regarding the effectiveness of the intervention to improve MSRF. Education (energy conservation and fatigue management) and exercise had supporting evidence for reducing MSRF but mixed conclusions gathered from subtypes of exercise. Reviews considering psycho-behavioural interventions (CBT and mindfulness) had limited information considering effectiveness. Finally, a single intervention combining physical and cognitive strategies showed more promising results.

Conclusion: Further research into Pharmacological interventions for MSRF is required notably considering the potential of Modafinil. Yoga~~, resistance and endurance training~~ and energy conservation/fatigue management programs ~~-~~had strong evidence supporting use in management of MSRF. Due to the dissimilar interventions used in combined training the subtype of exercise cannot be recommended. ~~despite initially concluding with "high~~ Future~~confidence"~~ Future research into Amantadine, psycho-behavioural interventions and ~~aerobic~~ endurance exercise is vital to justify the current National Institute for Health and Care Excellence ~~NICE~~ guidelines. The methodological quality of studies inhibited the ability of this review to provide other recommendations.

Comment [AS1]: Need for capitals?

Comment [AS2]: You give guidelines for endurance below – check

1:1.1 Introduction

Multiple Sclerosis related fatigue (MSRF) is reported in 70-80% of the MS population and over 55% of patients report fatigue as the worse symptom experienced from MS[1]. Compared to age and gender match controls, people who experience MSRF combined with other symptoms have significantly increased disability, reduced quality of life (physical and mental)[2] and reduced experiences of daily living[3]. For the purposes of this review we classify MSRF as fatigability (increased weakness after exercise or over the course of the day) or lassitude (abnormal feeling of constant tiredness)~~,~~[1~~2~~]. The main treatment for MSRF can be broadly classified as pharmacological or non-pharmacological ~~and~~ treatment for MSRF is directed by clinical guidelines e.g., in the UK by the National Institute for Health and Care Excellence ~~National Institute of Clinical Excellence~~ (NICE)[4~~4~~].

~~Currently~~ At present, amantadine is the only drug supported by the National Institute for Health and Care Excellence ~~NICE~~ guidelines for the pharmacological management of MSRF[4]. However, Prokarin is listed as an alternative medication, however only limited evidence justifies its effectiveness for treating MSRF[5]. Finally, Modafinil is not consistently licensed across westernised countries e.g., it is not ~~currently~~ licensed for the treatment of MSRF in the UK[6]. ~~One reason for this may be that~~ W~~w~~hilst some studies[7] have identified improvement in MSRF Methodological weakness and inadequate sample size of studies inhibit the ability to be conclusive about the results~~ the clinical evidence of the data is supporting the positive correlation significantly weak~~.

The National Institute for Health and Care Excellence ~~NICE~~ guidelines[4] advise education (energy conservation), exercise (aerobic, resistance and yoga) and psycho-behavioural techniques (Cognitive Behavioural Therapy (CBT) or mindfulness) as part of the non-pharmacological management of MSRF. ~~Current r~~Review evidence has identified short-term benefits of energy conservation on bio-psychosocial outcomes for patients with MSRF[8]. Many reviews have examined the effects of exercise on MSRF, however the heterogeneity of outcome measures used makes direct comparison between results difficult[9]. Prevailing ~~Current~~ research has not fully examined the effect of CBT on MSRF[10]. Mindfulness programs including tai-chi, yoga, relaxation and meditation found significant improvements in MSRF[11,12~~11~~]. Thus, evidence considering different non-pharmacological approaches requires further systematic consideration and synthesis.

Given the high volumes of the past review evidence across pharmacological and behavioural approaches that treat MSRF an overview review of recent evidence is required. To the best of the author's knowledge ~~,~~ to date, no review of reviews ~~systematic overview~~ of all approaches has been conducted. This review of reviews will summarise both pharmacological and non-pharmacological interventions for MSRF using novel synthesis techniques to provide clear intervention recommendations and provide prescription of treatment. ~~Thus t~~The aims of this research ~~is to provide a review of reviews that includes pharmacological and non-pharmacological reviews and to establish recommendations for the clinical treatment of MSRF.~~were to provide up-to-date evidence-based recommendations for the treatment of MS-related fatigue and to prioritise topics for future randomised clinical trials with sufficient power.

Methodology

Materials and Methods

An adapted PRISMA statement[1~~2~~3] was used to guide the systematic search processes and reporting.

Eligibility criteria

The following eligibility criteria was applied focusing on the eligibility criteria of the included reviews:

Comment [AS3]: Reword do you mean
Methodological weakness and inadequate sample size of studies inhibit the ability to be conclusive about the results.

- **Population:** Any group or sub-group (e.g., all sub-types of MS and in or outpatients, any time since diagnosis) of patients with MS was included. Note, a focus on the subtypes of MS is often lacking in review-based research[14~~3~~]. Reviews with multiple population groups were excluded unless a clear and separate analysis on patients with MS was undertaken.

- **Participants**: Male and female adults 18 years old and above were included. Paediatric patients were excluded due to physiological differences and alternative interventions often used[14~~5~~]. No animal studies were included.

- **Intervention:** Any pharmacological or non-pharmacological interventions designed to improve MSRF were included. Reviews that focused on interventions where treatment of MSRF was not a central or primary component were excluded.

- **Comparison Group**: Reviews were required to include education (active control) or no intervention (in-active control) to prevent a confounding bias[14~~3~~].

- **Outcome Measures:** Studies were included if a fatigue outcome measure or a measure of fatigue as a sub-domain of an outcome measure was used. A list of appropriate outcome measures can be seen in the Supplementary File.

- **Study design:** Any traditional quantitative systematic review focusing on effectiveness of treatments for MSRF from a peer-reviewed journal was included. Qualitative data was not included due to the focus on assessing effectiveness.

- **Other criteria:** (1) Time frame: Reviews from 2000 onwards were included. All relevant interventions ~~pre-2000~~pre-2000 we considered to be captured in the review evidence included[5] (2) Language: Reviews not written in English were excluded. (3) Grey literature: Unpublished reviews and conference proceedings were not included.

Search Strategy

Electronic databases were independently searched by ~~blind~~ researchers (PM, AS) from inception until May 2016. The following electronic databases were chosen; The Cochrane Library[~~15~~,~~CINAHL~~,16], CINAHL[~~16~~,~~17~~], PubMed/Medline[~~17~~,~~8~~], and Web of Science[18,19]. Pre-defined search terms with Boolean operators included: Multiple Sclerosis OR MS AND FATIGUE OR TIREDNESS OR EXHAUSTION OR LETHARGY OR LASSITUDE AND TREATMENT OR INTERVENTION OR EXPERIENCE AND REVIEW OR SYSTEMATIC REVIEW AND MEDICATION OR ALTERNATIVE THERAPY OR COMPLEMENTARY THERAPY OR THERAPY OR EXERCISE OR PHYSICAL ACTIVITY. Other search mechanisms included searching the reference lists of included reviews, searching the first 20 hits from pages of Google scholar and sciencedirect.com, and searching included author home research web pages. See Supplementary file for excluded reviews.

Study selection

Data extraction and collection procedures

Independent assessment of selected articles by PM/AS was undertaken when considering articles by title, abstract and full text. A third researcher could be contacted to arbitrate discussions where inclusion was not agreed. No arbitration was required.

PM collected data from each review including demographical information, methods, outcome measures of fatigue, number/type of studies, interventions and the results.

Critical appraisal of reviews

The AMSTAR (Assessment of the Methodological Quality of a Systematic Review) tool[19] and SALSA (Search, Appraisal, Synthesis and Analysis) tool[20] were used to assess the methodological quality of the systematic reviews. Both were combined to create a form used to assess quality (see

Supplementary File). The assessment of risk of bias conducted by reviews were grouped and a tabular of summary risk of bias created confirming with Cochrane's Collaboration Tool for Assessing Risk of Bias (See Supplementary File)[21]. A separate and combined grading analysis tool was created by PM (see Table 1) and allowed overall assessment of review quality as 'poor', 'fair', and 'good' within the below text. ~~,~~ ~~–~~The grading analysis tool was used to create confidence related statements by combining this data with the number of studies with supporting evidence from an intervention type. Three confidence and recommendation statements about intervention types were made including to use the intervention, (a) 'with caution', (b) 'with confidence' and (c) 'with high confidence' (See footnote in Supplementary File).

Domain of consideration	**Overall Assessment Grade given to Review**		
	Poor	**Fair**	**Good**
Outcome Measures	50% of outcomes have poor reliability and validity.	50% of outcomes have adequate reliability and validity.	90% outcomes have strong reliability and validity. Validation studies undertaken in Multiple Sclerosis populations.
Key Domains	1-2 domains	3-4 domains	5-6 domains
Results	Results contain no statistics and results are vague and unclear	Results contain some statistics and numeral value.	Results contain statistics, statistical analysis and meta-analysis
Risk of Bias	Unclear/N/A / High	Moderate, Moderate-High, Moderate-Low	Low
AMSTAR	0-4 Scoring	5-8 scoring	9-11 scoring

Table 1 Grading and review assessment criteria

Narrative Synthesis Processes

Two primarily synthesis techniques were used: (1) Tabulation was the main method of analysis in this review including a summary table of the included studies, listing of interventions and their results, outcome measures and methods[22]. (2) Translation of review findings was used to evaluate the key findings found from the results from each review to reach an overall conclusion that acted as the basis for recommendations. ~~We document t~~Two further analysis techniques are included~~ing~~ in the Supplementary File, this includes an event timeline was used to map the spread of reviews on interventions to view changes or trends in the literature and a taxonomic analysis that groups MSRF outcome measures together ~~in order to~~to identify the key MSRF domains[23]. Please note a traditional meta-analysis was not possible due to the heterogeneity of the data.

~~Results~~

Analysis of Evidence

Twenty-four reviews (195 ~~339~~ studies (Total number 324:129 duplicates)) were used in the data analysis (17 non-pharmacological, 5 pharmacological, 2 combining both) were included. The reviews were most often classified as systematic (n=19) or quantitative (n=11). A total of 19 reviews contained randomised controlled trials (RCT). Six reviews were restricted to only examining RCTs. The total number of participants included was 17,469 (17.8% male; 31.7% female; 50.4% unknown) with a mean age of 45.9 years and a mean age range of 8.3 years. Ten percent (n=1669/17469) had Relapsing-Remitting, 5.6% (1023/17469) had Progressive (Primary/secondary/unspecified) and 83 %

(13446/17469) were unknown. The average duration of MS was not clearly stated across reviews. In the majority (20/24, 83%) of reviews, the length of time of fatigue and its severity was unknown. A meta-analysis was conducted in six (6/24, 25 %) reviews. Duplicates of articles were included in the analysis as in some reviews the results were combined and presented as a concluding summary.

Outcome measures were categorised into the following domains of MSRF; Fatigue Severity and Extent, Physical Fatigue (Effects on ADLs, Exercise, Hobbies), Mental Fatigue (Psychosocial, Social, Distress), Vitality, Prevalence/Pattern of Fatigue and Qualitative Fatigue Data. Outcome measures that analysed more than one domain were placed in both groups. This was to be aware of the reviews which included studies with outcome measures that covered many of the domains or vice versa. It highlighted areas of fatigue that were not covered and could be included in future research.

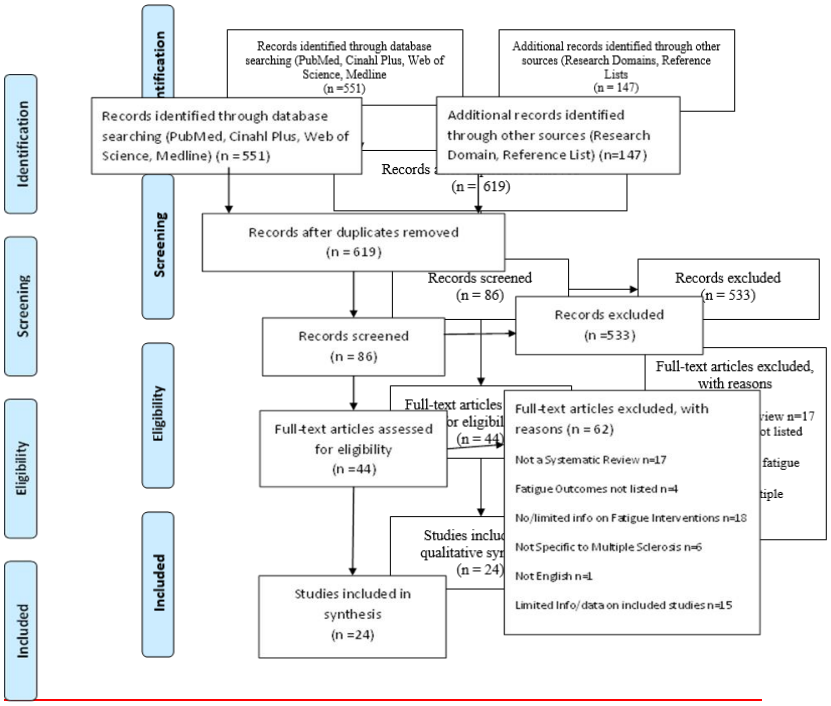

Figure 1 The PRISMA flow diagram (adapted from Moher et al., 2009)

Grading Criteria of Analysis

The AMSTAR score of the reviews is seen in Table 22. The mean scoring of the AMSTAR grading scale was 6.5 (SD=1.9: 95% CI=5.8-7.3). Three reviews were scored as low (0-4), 18 reviews were scored moderate (5-8) and 3 reviews were scored high (9-11).

All pharmacological reviews (n=7) had "fair" grading of analysis (Created by the author; see supplementary file). Majority of reviews (71%; 5/7) had "fair" outcome measures with 50% of outcome measures having adequate validity and reliability and "fair" key domains (86%; 6/7) and analysing 3-4 key domains. Lee[5] covered six key domains with included outcome measures. Four reviews[24,24,25,26,27] had "poor" results with vague or unclear results with no statistics. No reviews had "good" results, this had an impact on the specificity of the synthesis undertaken within this overview. Six reviews scored "poor" in reporting risk of bias, this meant results were unclear, had not assessed risk of bias or included studies had a high risk of bias. Brown[28,27] scored "poor" in the AMSTAR score.

In non-pharmacological reviews, the majority had a "fair" grading apart from two reviews[28,29] which were regarded as "poor". Majority of reviews (84%; 16/19) had "fair" outcome measures with 50% of outcome measures having adequate validity and reliability and "fair" key domains (79%; 15/19) -with the outcome measures analysing 3-4 key domains. Two reviews[30,5] covered six key domains with included outcome measures. Five reviews had "poor" results with unclear or vague results and no statistics. Five reviews,[2,8,32,21,,32,34,33] had "good" results with statistical analysis and meta-analysis. Eight reviews[9,24,33,29,28,32,21,35,4,,35,36,37,38] scored "poor" and two reviews[29,30,28] scored "good" risk of bias. Two reviews[28,37,6] scored "poor" in the AMSTAR score and three reviews[31,10,31,32,39,7] had "high" AMSTAR score.

Table 2-Analysis of the Methodological Quality of the Reviews

Review (First Author)	Outcomes	Key Domains (n= x/6)	Risk of Bias	AMSTAR (n = x/11)
Branas[34]	Qualitative, Preferred treatment, MS-FS, FSS,RIV,VAS, FIEDL,DFE	5	Unclear	7
Brown[27]	FSS,EDSS,VAS,FAI, MFIS	3	N/A	2
Lee[5]	VAS,MFIS,FSS, Epworth Sleep Scale, MSQOL,MFI, SF-63,FIS,DFE	6	Mod/ Low	5
Pucci[23]	EDSS,VAS,Preferred treatment, MS-FS, RIV,FSS,FIS	4	High	6
Taus[24]	Preferred treatment,VAS, EDSS,RIV,FSS,MS-FS	4	High	6
Tejani[25]	FSS,FIS	3	Unclear	8
Tejani[26]	FSS,FIS,VAS,MFIS,SIP	3	Unclear	8
Andreasen[9]	CFS,MFIS,FSS,MFI, qualitative	4	N/A	5
Asano[25]	MFIS,FSS,MFI,VAS, FIS,FS,FAI	3	N/A	6
Blikman[8]	MFIS,FSS,IPA, FIS,MSFS,SF-36	5	Mod /Low	7
Branas[34]	Not included	5	Unclear	7
Cramer[31]	MSQOL,MSIS,SF-36,FSS,MFIS,MFI	3	High	7
Dalgas[29]	Unclear	0	Low	6

Heine[32]	FSS,MFIS,MFI,VAS,SF-36, MSQOL,FSMC,POMS	4	Moderate	10
Karpatkin[36]	(in 5 studies) ODI, FSS,FIS,FDI,MSIS	3	N/A	4
Khan[30]	SF-36,VAS,MS-QOL, Fatigue Frequency, EDSS,FIM,MSIS,FIS,FSS	6	Mod/ High	9
Khan[37]	(5studies) MSIS,FSS,FIS,SF-36, MFIS	4	High	10
Latimer-Cheung[2]	SF-36, POMS,MSQOL, FSS,MFIS	4	Mod/ Low	6
Lee[5]	VAS,MFIS,FSS, Epworth Sleep Scale,SQOL,MFI, SF-63,FIS,DFE	6	Mod/ Low	5
Malcomson[38]	POMS, SF-36, MSIS, MSQOL	3	Low	6
Pilutti[33]	FSS,MFIS,MSQOL,SF-36.POMS,MFI, SIP	4	Mod/ High	7
Plow[26]	SF-36, FIS,MFIS	4	N/A	3
Rietberg[39]	EDSS,SF-36,FSS, MSIS,FAMS,SIP,FIM	4	Mod	7
Simpson[40]	SF-36	1	Mod/ High	7
Steultjens[11]	FIS,SF-36	3	Mod	7
Thomas[10]	MSQOL,SF-36, HRQOL,FAI,SIP,EDSS, MAFS	4	Unclear	8

Review	Description	Number of Studies	Types of Studies	Methods Described (SALSA)				AMSTAR Score
				Search	Appraisal	Synthesis	Analysis	
Andreasen, 2011	Systematic Review of the Literature	23 articles (21 trials)	RCT: 10 CT: 3 UC:8	8 Databases	None	Narrative, Tabular, Qualitative	Descriptive	5/11
Asano, 2014	Review	25	RCT:25	4 Databases	Effect Size	Narrative, Tabular	Descriptive	6/11
Blikman, 2013	Systematic Review of RCTS and CCT	6	RTC: 4 CT:2	4 Databases	Risk of Bias using a Furlan et al quality criteria list	Narrative, Tabular,	Meta-analysis using Forest Plots for Statistical Heterogeneity Descriptive.	7/11
Branas, 2000	Scoping Review	15	RTC: 9 CT: 2 UC: 4	7 Databases, 1 publication, 3 websites and contacted experts	Assessment of Validity was based on Jadad Scale. Cochrane Risk of Bias	Narrative, Tabular	Meta-analysis using RevMan 4.0.4 software	7/11
Brown, 2010	Literature Review	6	UC:6	2 Databases	None	Narrative, Tabular	Descriptive	2/11
Cramer, 2014	Systematic Review of RCTs, RCOT, CRT	7	RCT:7	7 Databases, 2 Journals	Cochrane Risk of Bias	Tabular, Narrative,	Meta-analysis using review Manager 5 software. Hedges's correction for small study samples, Statistical heterogeneity using the I2 statistics. Risk of Bias across studies. Review Manager software, sensitivity analysis.	7/11

Dalgas, 2015	Systematic Review of RCTs	15	RCT:15	8 Databases	PRISMA, PICO, PEDro scoring	Tabular, Narrative	Meta-analysis using Meta-Analysis of Observational Studies in Epidemiology Framework, Forest Plot of the individual studies unable to be meta-analysed.	6/11
Heine, 2015	Cochrane Systematic Reviews of RCTs	45	RCT:45	8 Databases	Cochrane Risk of Bias, PEDro scale, Cochrane Handbook for Systematic Reviews of Interventions. Methodological quality of studies using the GRADEpro software.	Tabular, Descriptive, Narrative	Meta-analysis, Forest Plot of assessment of heterogeneity, Sensitivity analysis. Funnel Plots for assessing publication bias	10/11
Karpatkin, 2014	Systematic Literature search	15 (14 trials) (3 on fatigue)	UC:3	3 Databases	None	Descriptive, Tabular	Descriptive	4/11
Khan, 2007	Cochrane Systematic Review of RCT and CCT	13	RCT:11 CT:2	7 databases, Authors, relevant journals, unpublished trials	Cochrane Handbook for Systematic Reviews of Interventions. Review Manager software developed by the Cochrane Collaboration, Cochrane Risk of Bias	Tabular, Descriptive, Narrative	Sensitivity analysis, investigation of heterogeneity	9/11
Khan, 2015	Cochrane Systematic Review of RCT and CCT	9	RCT:9	7 Databases, journals, ongoing and unpublished trials	Methodological quality of studies using the GRADEpro software. Review Manager 5 software developed by Cochrane, Cochrane Risk of Bias	Narrative, Descriptive	Heterogeneity analysis, unit of analysis, sensitivity analysis (Grade)	10/11
Latimer-Cheung, 2013	Systematic Review of the	54 (30 on fatigue)	RCT:11 CT:12	7 Databases	PEDro for study quality in RCTS and Downs and Blacks for	Narrative, Descriptive, Tabular	Cochrane Handbook for Systematic	6/11

		Literature				NRCTs		Reviews of Interventions for descriptive synthesis	
Lee, 2008		Systematic Review of the Literature	15	RTC: 9 CT:4 UC:2	12 Databases	Quality of studies reviewed (unknown)	Narrative, Tabular	Descriptive	5/11
Malcomson, 2007		Systematic Review of the Literature	33	RCT:9 CT: 16 UC:8	16 Databases	Downs and Black Quality Checklist.	Narrative, Descriptive	Descriptive	6/11
Pilutti, 2013		Quantitative synthesis of randomized controlled trials	17	RTC: 17	4 Databases	PEDro	Narrative Descriptive	Meta-analysis of Observation Studies in Epidemiological framework. ESs for each study were entered into the Comprehensive Meta-Analysis software, Heterogeneity of the overall ES	7/11
Plow, 2013		Scoping Review	34 articles (27 interventions)	RTC:13 CT:6 UC:8	3 Databases, 4 journals	None	Tabular, Descriptive	Descriptive	3/11
Pucci, 2007		Cochrane Systematic Review of the Literature	5	RCT:5	5 Databases, 4 journals	The scoring for allocation concealment, Jadad's scale, Cochrane Risk of Bias	Descriptive, Narrative	Descriptive	6/11
Rietberg, 2005		Cochrane Systematic Review of the Literature	9	RCT:9	7 Databases, 1 journal	Methodological quality assessment (11 scoring system), kappa statistics Cochrane Methodological Quality of	Tabular, Descriptive, Narrative	Descriptive	7/11

						Included Studies			
Simpson, 2014	Systematic Review of Evidence	3	RCT:2 CT:1	7 Databases	SPIO-study design, Cochranes Collaboration for Risk of Bias	Tabular, Narrative	Descriptive	7/11
Steultjens, 2003	Cochrane Systematic Review	3	RCT:1 CT:1 UC:1	9 Databases, authors	Methodological quality by list of Van Tulder List. Cochrane risk of bias	Descriptive, Narrative, Tabular	Descriptive. Standardised mean differences. Odds ratios, Sensitivity analysis	7/11
Taus, 2003	Cochrane Systematic Review	4	RCT:4	1 Database, 4 Journals	Methodological Quality of the Cochrane Checklist	Narrative	Descriptive	6/11
Tejani, 2010	Cochrane Systematic Review	1	RCT:1	4 Databases, 4 journals	Cochrane Risk of Bias, Quality Checklist	Tabular, Narrative	Forest Plot of Heterogeneity analysis, Sensitivity Analysis	8/11
Tejani, 2012	Cochrane Systematic Review	2	RCT:2	5 Databases	Quality Checklist, Cochrane Risk of Bias,	Descriptive, Tabular, Narrative	Heterogeneity and descriptive analysis (Forest Plot)	8/11
Thomas, 2006	Cochrane Systematic Review	17	RCT:17	19 Databases, trials in progress	Cochrane Allocation Concealment	Tabular, Descriptive, Narrative	Data Extraction tool, Meta-analysis of mini-reviews, Homogeneity Analysis (Chi-squared/Odds ratio/Mantel-Haenszel)	8/11

Abbreviations: CT: Controlled Trial, RCT: Randomised Control Trial, UC: Uncontrolled Trial

ResultsTable 2 Grading criteria used to assess overall quality of the reviews

Note: Abbreviations. CFS=Chandler's fatigue scale, DFE= Diary of Fatigue Experience, EDSS= Expanded Disability Status Scale, FAI=Fatigue Assessment Instrument, FAMS=Functional Assessment of Multiple Sclerosis, FDI=Function and Disability Inventory, FIEDL= Fatigue Inventory of Effects on Daily Living, FIM= Functional Independence Measure, FIS=Fatigue Impact Scale, FSS=Fatigue Severity Scale, FSMC=Fatigue Scale for Motor and Cognitive Functions, HRQOL-MS=Health Related Quality of Life for Multiple Sclerosis, IPA, Impact on Participation and Autonomy, MAFS=Multidimensional Assessment of Fatigue Scale, MFI=Multidimensional Fatigue Inventory, MFIS=Modified Fatigue Impact Scale, MS-FS=Multiple Sclerosis Functional Score, MSQOL=Multiple Sclerosis Quality of Life, MSIS=Multiple Sclerosis Impact Scale, ODI= Oswestry disability index, POMS=Profile of Moods States, RIV= Rand Index of Vitality, SEP59=Multiple Sclerosis Quality Of Life scale, SF-36=Short Form-36 Vitality Subscale of the Short Form Health Survey, SIP=Sickness Impact Profile, SPFS=Subjective Perception of Fatigue Scale, VAS-Visual Analogue Scale. In Branas (2000) only pharmaceutical interventions included the relevant outcome measures.

Tabulation and Translation of Findings of Interventions

.In total Fifty-five pharmacological and non-pharmacological grouped interventions were found in this review. The results of the interventions are listed in Table 3 and 4. Below the outcome measures are categorised into the following domains of MSRF; Fatigue Severity and Extent, Physical Fatigue (Effects on ADLs, Exercise, Hobbies), Mental Fatigue (Psychosocial, Social, Distress), Vitality, Prevalence/Pattern of Fatigue and Qualitative Fatigue Data. Outcome measures that analysed more than one domain were placed in both groups.

Pharmacological Interventions

In total, seven reviews examined the pharmacological interventions available (see table 3):

Summary and recommendation for pharmacological interventions

Evidence is reported by drug type below:

(a) Amantadine was identified as not significantly affecting fatigue in 66% (10/15) of the included ~~reviews~~studies. Where significant change was identified (4/15) this was identified within the following domains: Mental Fatigue (4/4; 100%), Physical Fatigue (4/4; 100%), Fatigue Severity and Extent (4/4; 100%), Vitality (4/4; 100%) and Prevalence and Pattern (1/4; 25%)

(b) Pemoline had conflicting results from two reviews with ~~the majority of~~most studies (3/4; 75%) concluded insignificant effects on MSRF. The included key domains were Mental Fatigue (2/2; 100%), Physical Fatigue (2/2; 100%), Fatigue Severity and Extent (2/2; 100%), Vitality (2/2; 100%) and Prevalence and Pattern (1/2; 50%).

(c) Modafinil was identified to have significant improvement on fatigue in 75~~1~~ % of studies (6~~5~~/8~~7~~) in 2 reviews. The included key domains were Fatigue Severity and Extent (2/2; 100%), Mental Fatigue (2/2; 100%), Physical Fatigue (2/2; 100%), Prevalence and Pattern (1/2; 50%) and Vitality (1/2; 50%).

(d) Prokarin was only considered within one pilot study[5] where a significant improvement in MSRF was reported. The key domains covered in the single study were unknown.

(e) Carnitine was identified to have ~~inconclusive~~ insignificant results on MSRF in the two included reviews. The included domains were Fatigue Severity and Extent (2/2; 100%), Physical Fatigue (2/2; 100%) and Mental Fatigue (2/2; 100%).

(f) Pemoline combined with aspirin found an improvement in MSRF in one study in Lee~~, et al.,~~[5] but the key domains of were not detailed.

There are currently no reviews assessing the effects of Aminopyridine[3,4] Diaminopyridine, Interferon Beta 1b and antidepressants on fatigue improvement in MS[5,7]. This could be an area in future research that could be investigated.

Intervention	Review (First Author)	Results of Within Reviews	Summary of Significant results and side effects
Amantadine	Asano [3,5]	**Significant Results:** None found	**Significant Results**: 3 reviews[34,24,5] reported significant fatigue improvements. However, 4/9 of the studies[34,24] contained data of limited quality. Therefore, 5/15 studies reported fatigue improvement with amantadine **Side effects:** Average of 40% participants in 4 studies reported adverse side effects.
		Non-Significant Results: ES for Amantadine−0.59 (95%CI: −1.26 to 0.06). 5 studies* found no significant effects	
		Side Effects Identified: None reported	
	Branas[3,5,4]	**Significant Results**: Four studies** (n=236) concluded improvement in MS fatigue. One did not define fatigue symptoms and had limited information. Another examined fatigue effects with VAS (p>0.05) and others used MS-FS (P=0.04), FSS (P=0.33) and Daily Rating Point Scale (p=0.58).	
		Non-Significant Results: The clinical significance examined in one study looking at activities of daily living. A validated outcome measure not used so results were inconclusive.	
		Side Effects Identified: 20-60% participants reported side effects but no significant difference between studies against placebo. Side effects included sleep disturbances, palpations, insomnia, headaches, nausea and constipation.	
	Taus[2,5,4]	**Significant Results:** In 3 studies**, 30.3% of respondents preferred amantadine (n=183). One study had 60% of respondents preferred amantadine but these were the only responders (total n=10).	
		Non-Significant Results: Subjective improvement in fatigue in the final study** but results expressed as patient preference so data could not be summarised.	
		Side Effects Identified: 40% of participants compared to 35.5% placebo reported side effects (hallucinations, nausea, hyperactivity, anxiety and insomnia). Less than 10% of participants dropped out because of adverse effects.	
	Pucci[2,4,3]	**Significant Results: None**	
		Non-Significant results: Subjective improvement in fatigue with amantadine in 5 studies ** (n=190) but insufficient data to justify.	
		Side Effects Identified: Side effects reported in 40% of participants in one study with a dropout rate of 28% and another over 40% of participants had side effects (hallucinations, nausea, hyperactivity, anxiety and insomnia).	
	Lee[5]	**Significant Results:** ~~Two studies (n=110~~One study~~)~~* concluded improvement in MS fatigue. One study found fatigue improved (p<0.01) in 115 out of 165 participants.	
		Non-Significant Results: The remaining study examined the neurophysiological measures of fatigue compared against a placebo, amantadine and pemoline but no significant differences found.	
		Side Effects Identified: All studies reported adverse effects. Twenty one percent (n=165) of participants reported insomnia with taking amantadine.	
Pemoline	Branas[3,5,4]	**Significant Results: None**	**Significant Results**: Subjective fatigue improvement in 1 study in one review[5] **Side effects:** 3/4 studies
		Non-Significant Results: Two studies* found no improvement in fatigue with Pemoline against a placebo. None examined clinical effects of pemoline on quality of life. One found no significant difference between pemoline and placebo (p>0.05) and the other had negative effects on FSS outcome measure and positive on the MS-FS outcome measure but neither were significant (p=0.845 and p=0.394).	

		Side Effects Identified: Both studies reported adverse effects with pemoline. In one study the number of participants with side effects was unknown. In the other >25% reported side effects (irritability, insomnia, nausea and anorexia).	reported adverse side effects. 25% participants reported effects in one study and another 26% dropped out because of effects
	Lee[5]	**Significant Results:** ~~½~~ 1 /2studies (n=46) had 46.3% of participants achieving "excellent or good" fatigue relief with pemoline compared to 19.5% with placebo (p=0.06).	
		Non-Significant R~~r~~esults: 1/2 studies* (n=126) found no significant changes in neurophysiological measures with placebo, pemoline or amantadine.	
		Side Effects Identified: In one study (n=46) 26% of patients dropped out of the study due to adverse side effects (anorexia, irritability and insomnia). Side effects not reported in the other study.	
Modafinil	Asano[3~~6~~5]	**Significant Results:** 1 study* found a significant effect on MSRF.	**Significant Results:** 6~~5~~/8 ~~7~~ studies found significant fatigue improvement with Modafinil **Side effects**: Reported in 1 reviews [27]3 studies reported adverse effects and in 2 ~~studies there~~studies there was a 5-29% dropout rate because of this.
		Non-Significant Results: ES was 0.55 (95%CI: −0.06 to 1.16). 1/2 studies had no significant effect on MSRF	
		Side Effects Identified: None reported	
	Lee[5]	**Significant Results:** 1/2 studies* (n=72/187) found that FSS scores decreased (0<0.001) and MFIS (P<0.001) and VAS (p=0.003).	
		Non-Significant R~~r~~esults: One study (n=115) had improvements in the MFIS with modafinil and the placebo (52.3 +- 18.5 versus 49.2+-16.6) but no significant differences between treatments (p=0.27). Both studies are reviewed by Brown[12].	
		Side Effects Identified: None reported	
	Brown[2~~8~~7]	**Significant Results:** Five studies*-(n=308). Short-term efficacy (12 weeks) in fatigue improvement (22% reduction in symptoms seen in 4 uncontrolled studies of patient taking 200mg or less of modafinil). One study (n=55) found an improvement in the FSS (P<0.001) and in the Epworth Sleepiness Scale (P<0.001) compared to baseline. One study found 50% of participants (n=33) had improvement in VAS score compared to baseline. One study examined MS (n=17) with other neurological conditions found a significant improvement in FSS (P=0.006) but not in the Epworth Sleep Score(p<0.05). Another study (n=72) found FSS scores decreased (p<0.001) and in MFIS (P<0.001) and VAS (p=0.003). One study (n=115) had improvements in the MFIS with modafinil and the placebo (52.3 +- 18.5 versus 49.2+-16.6) but no significant differences between treatments (p=0.27). The fifth study (n=21) found lower FSS than baseline results when comparing against a placebo (p=0.023).	
		Non-Significant R~~r~~esults: None	
		Side Effects Identified: In one study (n=55) 3 patients dropped out due to adverse effects (nervousness and increased vertigo). In another (n=17) 5 patients dropped out due to side effects (headache, excitability and hypertension=seen in all neurological patients in the study). In one study (n=72) adverse effects reported were headache, nausea and asthenia).	
Prokarin	Lee[5]	**Significant Results:** Improvement in MS fatigue was seen in a pilot study (n=22) with Prokarin. MFIS mean was significantly different from the placebo (p=0.02).	**Significant Results:** Fatigue improvement seen in 1 pilot study **Side effects:** Not reported
		Non-Significant R~~r~~esults: None	
		Side Effects Identified: Adverse effects not recorded	

Carnitine	Tejani[26]	**Significant Results: None**	**Significant Results:** None **Side effects:** Not reported
		Non-Significant ~~r~~Results: No studies* found clear results on Carnitine when compared with amantadine due to an adverse event resulting in 18 patients dropping out (n=36) (Relative Risk Ratio 0.20. 95%CI	
		Side Effects Identified: Adverse effects not recorded	
	Tejani[27]	**Significant Results: None**	
		Non-Significant ~~results~~Results No studies* found clear results on Carnitine when compared with amantadine. Adverse event resulted in 18 patients dropping out (n=36) (Relative Risk Ratio=0.20.95%CI). Review analysed the same study as Tejani[15] as there were no other finished trials at the time of analysis.	
		Side Effects Identified: Adverse effects not recorded	

Table 3 Pharmacological interventions and supporting evidence form review

Note: ~~ indicates review was deemed poor quality through critical appraisal process~~. Abbreviations. CFS=Chandler's fatigue scale, DFE= Diary of Fatigue Experience, ~~EDSS= Expanded Disability Status Scale,~~ FAI=Fatigue Assessment Instrument, FAMS=Functional Assessment of Multiple Sclerosis, FDI=Function and Disability Inventory, FIEDL= Fatigue Inventory of Effects on Daily Living, FIM= Functional Independence Measure, FIS=Fatigue Impact Scale, FSS=Fatigue Severity Scale, FSMC=Fatigue Scale for Motor and Cognitive Functions, HRQOL-MS=Health Related Quality of Life for Multiple Sclerosis, IPA, Impact on Participation and Autonomy, MAFS=Multidimensional Assessment of Fatigue Scale, MFI=Multidimensional Fatigue Inventory, MFIS=Modified Fatigue Impact Scale, MS-FS=Multiple Sclerosis Functional Score, MSQOL=Multiple Sclerosis Quality of Life, MSIS=Multiple Sclerosis Impact Scale, ODI= Oswestry disability index, POMS=Profile of Moods States, RIV= Rand Index of Vitality, SEP59=Multiple Sclerosis Quality Of Life scale, SF-36=Short Form-36 Vitality Subscale of the Short Form Health Survey, SIP=Sickness Impact Profile, SPFS=Subjective Perception of Fatigue Scale, VAS-Visual Analogue Scale. *1-3 duplicate articles within findings, **4-6 duplicate articles within findings, *** 7+ articles*

Comment [AS4]: Delete this?

Non-Pharmacological Interventions

Forty-six non-pharmacological interventions were found from the reviews. Table 4 provides a summary of this evidence.

Summary and recommendation for non-pharmacological interventions

Evidence is reported by intervention type below: Many reviews grouped exercise interventions to conclude an overall outcome. Individual exercises were not examined due to an inability to compare because of the heterogeneity of the data. The subtype of exercise was not examined in Rietberg[40~~39~~], but an overall improvement in MS fatigue was seen with exercise interventions although statistical data was not included. The key domains covered in the review were Physical Fatigue, Vitality, Fatigue Severity and Extent and Mental Fatigue.

~~-~~*(a)* Endurance training was identified to have a significant improvement in MS in four reviews (19/374 studies, ~~79~~51%). ~~In particular~~ Heine[33~~22~~] conducted a meta-analysis of 12 studies and a significant effect on fatigue was concluded (SMD-0.43, 95% CI -0.69 to -0.17; P < 0.01). The included key domains were Mental Fatigue (3/4; 75%), Physical Fatigue (3/4; 75%), Fatigue Severity and Extent (3/4; 75%) and Vitality (2/4; 50%).
~~-~~*(b)* Resistance training was identified to have a significant improvement on MSRF in six reviews (136/1930; ~~53~~68%). The included key domains were Vitality (3/6; 50%), Mental Fatigue (5/6; 83%), Physical Fatigue (5/6; 83%) and Fatigue Severity and Extent (5/6; 83%).
~~-~~*(c)* Aerobic training identified an improvement on MSRF in three reviews (116/106; 680%). The key domains were Mental Fatigue (3/3; 100%), Physical Fatigue (3/3; 100%), Fatigue Severity and Extent (3/3; 100%) and Vitality (3/3; 100%). Malcomson[38] was not considered in the results as fatigue was not examined as an outcome.
(d) Combined training (multiple exercise types used) identified an improvement on MS fatigue in five reviews (~~13~~20/23~~/25~~; 87~~52~~%). The included key domains were Fatigue Severity and Extent (4/5; 80%), Mental Fatigue (4/5; 80%), Physical Fatigue (4/5; 80%) and Vitality (3/5; 60%).
~~-~~*(e)* Yoga identified a significant reduction on MSRF in seven reviews (18/22; 81%). The included key domains were Fatigue Severity and Extent (6/7; 86%), Mental Fatigue (6/7; 86%), Physical Fatigue (6/7; 86%), Prevalence and Pattern (1/7; 14%) and Vitality (4/7; 57%).
(f) CBT and other behavioural interventions (mindfulness and tele-rehabilitation) identified an improvement on MS fatigue in 5 reviews (~~5/18~~10/22; 45~~27~~%). The key domains were Mental Fatigue

(3/5; 60%), Physical Fatigue (3/5; 60%), Vitality (4/5; 80%) and Fatigue Severity and Extent (2/5; 40%).

~~(g)~~ Energy conservation and fatigue programs identified an improvement on MS fatigue in six reviews (2~~62~~/2~~69~~; ~~76~~100%). The key domains were Mental Fatigue (6/6; 100%), Physical Fatigue (6/6; 100%), Vitality (5/6; 83%) Prevalence and Pattern (1/6; 17%), and Impact on Participant and Autonomy (1/6; 17%) and Fatigue Severity and Extent (4/6; 67%). (g) MDR identified a significant improvement on MS fatigue in three reviews (3/6; 50%). The key domains were Mental Fatigue (3/3; 100%), Physical Fatigue (3/3; 100%), Fatigue Severity and Extent (3/3; 100%), Prevalence and Pattern (1/3; 33%) and Vitality (2/3; 67%).

(h) Acupuncture identified an improvement on MS fatigue in one review. The key domains were Mental Fatigue, Fatigue Severity and Extent and Physical Fatigue.

Comment [AS5]: Needed?

Intervention	Review (First Author)	Results of Within Reviews	Summary of Significant results
Endurance Training	Branas[32~~4~~]	**Significant Results: None**	**Significant Results:** 19/3~~7~~4 studies concluded an significant improvement on MSRF with endurance training
		Non-Significant results:1 study but the results are not discussed.	
	Andreasen[9]	**Significant Results:** 5~~4~~/11~~7~~ studies* (n=173) concluded significant improvements in fatigue. Studies examined ergometer bicycling (n=8 FSS p=0.058 pre and post ~~intervention)(~~intervention) (n=36 -MFIS p<0.05)(n=14 p=<0.05 when compared against active control)(n=15 p<0.01).	
		Non-Significant results: 6~~3~~/11~~7~~ studies* concluded no significant effect.	
	Heine[3~~22~~]	**Significant Results:** 17 studies* used endurance interventions and 2/7 concluded a significant effect. 11 studies used in meta-analysis (n=156 participants versus n=110 control) and a significant effect concluded (SMD=-0.43, 95% ~~CI, -~~CI, -0.69 to -0.17, p<0.01).	
		Non-Significant results: 5/7 studies* included in Andreas~~e~~e~~n~~[~~89~~] concluded no effect on fatigue.	
	Dalgas[30~~29~~]*	**Significant Results:** 3/9 studies* previously included in Andreasen[~~89~~] and Heine[3~~320~~]. Statistical data not included but 4 studies reported an improvement in fatigue (1 temporary and 1 incomplete data).	
		Non-Significant results: 4/9* concluded no effect.	
Resistance Training	Andreasen[9]	**Significant Results:** 3/~~7~~ studies**~~5~~ (randomised trials) contained statistical data (n=31). In one study 7/8 participants reported decreased fatigue and 2 studies found significant effects on ~~fatigue -(~~fatigue (p<0.05 and p<0.04).	**Significant Results:** 13/~~16/30~~19 studies concluded a significant improvement on MSRF with resistance training
		Non-Significant results: ~~None~~4 studies did not contain statistical information.	
	Latimer-cheung[2]	**Significant Results:** Levels of evidence discussed in the aerobic training section. A study (level 1 evidence) concluded significant improvement in general fatigue with a ~~12 week~~12-week program. 3 studies** (level 4 evidence) reported decreased mental and physical fatigue after a 8-10 week program.	
		Non-Significant results: None	
	Pilutti[34~~3~~]	**Significant Results:** 3 studies** listed as solely resistance training. Beneficial effect on MS fatigue concluded (0.42(-0.26 to 0.96)) (0.48(N/A)) (0.09(N/A)).	
		Non-Significant results: Resistance training~~s~~ studies were~~as~~ unclear.	
	Dalgas[30~~29~~]*	**Significant Results:** 2 studies** examining the effects of resistance training (n=34). 1 study in Andreasen[~~98~~]. Statistical data not included but one study showed weak but significant improvement in MS fatigue.	
		Non-Significant results: None	
	Asano[3~~65~~]	**Significant Results:** 1 ~~6~~ study** had significant positive effect on MSRF~~ics~~ (ES 0.81 CI=0.08–1.15)~~had a mean ES 0.63 (0.31–0.88) compared to control ES 0.16(−0.003–0.79). When applying 95%CI 1 studies had significant results.~~	
		Non-Significant results: 2 studies had no significant effect (ES 0.24 CI=1.15–0.64; ES 0.20 CI=0.60–1.02)~~5/6 studies had non-significant effects when compared against the control~~	

	Heine[3~~23~~]	**Significant Results:** 2/8 trials** ~~included in Andreasen[8] and Dalgas[19].~~ 4 trials** in the meta-analysis (n=146 participants versus 61 control) showed a heterogeneous (p=0.02) non-significant effect versus a control. The standard mean deviation (SMD) combined with SMD of the best powered trial concluded resistance training could impact fatigue by 0.3 points on the FSS (95% CI-6.3 to 6.9) or 0.5 points on the MFIS (95%CI 11.2-12.3).	
		Non-Significant R~~r~~esults: None	
Aerobic Training	Branas[3~~54~~]	**Significant Results:** 1 RCT* concluded moderate aerobic exercise might be beneficial in fatigue management. ~~None~~	**Significant Results:** 11~~6~~/16~~0~~ studies found a significant improvement on MS fatigue with aerobic training
		Non-Significant R~~r~~esults: ~~1 RCT concluded moderate aerobic exercise might be beneficial in fatigue management.~~None	
	Pilutti[34~~3~~]	**Significant Results:** ~~.~~ One study* found significant benefit of aerobic exercise on fatigue (ES=1.27(0.29-2.25).	
		Non-Significant R~~r~~esults: 5/6 studies* had the lowest effect size of all studies examined (ES -0.26) ~~but the studies were not individually listed so cannot be examined~~. Mixed conclusions on effects of training so 5 of the studies had insignificant results	
	Latimer-Cheung[2]	**Significant Results:** ~~13~~ 8 studies* examined fatigue changes in aerobic training. The included studies were assessed for their "level of evidence" (levels 1-4). (Level 1= RCT studies with PEDRO score >6.) 5~~3~~ RTCs (level 1 evidence) reported significant improvement in fatigue symptoms but not specific to MS fatigue. 3~~1~~ study (level 4 evidence) concluded significant improvements in fatigue with a 8 week aerobic program.	
		Non-Significant R~~r~~esults: ~~Statistical data pre and post intervention not included for fatigue. The 9/13studies concluded no significant changes in fatigue.~~None	
	Asano[36]	**Significant Results:** ES for ranged from −0.24 (95%CI: −1.15 to 0.64) to 2.05 (95%CI: 1.00–3.11). After taking 95%CI into consideration, only one aerobic study* presented a significant intervention effect	
		Non-Significant Results: None	
Combined Training	Andreasen[9]	**Significant Results:** 2/5 studies* (total n=97) found a significant improvement in fatigue with combined training (n=9 p=0.01 Pre/post 46+-6.3/39.4+-3.4) (n=12 p=0.02). 1 study recording qualitative data found combined training correlated with improvements in fatigue (n=10).	**Significant Results:** 20~~13~~/23~~5~~ studies found a significant improvement on MS fatigue with combined training
		Non-Significant R~~r~~esults: The final 2/5 studies found no significant effect on fatigue.	
	Pilutti[34~~3~~]	**Significant Results:** None	
		Non-Significant R~~r~~esults: Unclear which studies had mixed modalities of training. Inconsistency between the results and effect of combined training on fatigue inconclusive.	

	Latimer-Cheung[2]	**Significant Results:** 5 studies* reported significant changes in fatigue with a combined training program. 2 studies contained level 1 evidence and 3 contained level 4 evidence. Levels of evidence are discussed in the aerobic training section.	
		Non-Significant Results: None	
	Dalgas[30,29]*	**Significant Results:** None	
		Non-Significant Results: 2 studies (n=32) found no improvements in fatigue or depressive symptoms. Statistical data was not included.	
	Heine[33]	**Significant Results:** 13 studies* had endurance and power aspects. 6 studies (n=319 participants versus 176 control) included in meta-analysis. Significant effect on fatigue with combined training (SMD-0.73, 95%CI-1.23 to -0.23 P<0.01). The SMD combined with SD of the best powered trial and found fatigue can improve to -7.1points on FSS (95%CI-11.9 to -2.2) and on the MFIS (95% CI-21.3 to-4.0).	
		Non-Significant Results: None	
Yoga	Lee[5]	**Significant Results:** 1 study*** concluded some benefit on fatigue. Statistical data was not available	**Significant Results:** 18/22 studies reported. 2 additional studies reported some benefit with yoga but the details were not clear so marked as insignificant.
		Non-Significant Results: None	
	Pilutti[34]	**Significant Results:** 2 studies*** found significant effect on fatigue. Average effect size 1.27(1.12-1.42) and 0.20(-0.20-0.62).	
		Non-Significant Results: None	
	Latimer-Cheung[2]	**Significant Results:** 1 study*** concluded some benefit on fatigue. Statistical data not available	
		Non-Significant results: None	
	Cramer[32]	**Significant Results:** Meta-analysis (7 studies*** n=670) concluded that yoga improved short-term fatigue compared to usual treatment (SMD=-0.52.95%CI. P=0.06).	
		Non-Significant Results: None	
	Heine[33]	**Significant Results:** 7 studies*** investigated the effects of yoga on fatigue. ~~1 studies examined by Dalgas[19] and 5 were included in Cramer[18].~~ The results combined into "other training". The mean fatigue outcome ES was 0.54 standard deviations lower (0.79 to 0.29) suggesting that yoga has beneficial effects on fatigue.	
		Non-Significant Results: None	
	Dalgas[30,29]*	**Significant Results:** 2 studies*** found no effect of yoga on fatigue. Statistical data not available.	
		Non-Significant Results: None	

		Asano[3~~5~~]	**Significant Results:** ~~2 studies mean ES of 0.535 compared to control 0.6. With 95% CI no studies were statistically significant~~ None~~.~~	
			Non-Significant R~~r~~esults: 2 studies*** mean ES of 0.535 compared to control 0.6. With 95% CI no studies were statistically significant ~~None~~	
Behavioural Interventions		~~Steultjens[11]~~Steultjens[12]	**Significant Results:** None	**Significant Results**: 10~~5~~/22~~18~~ studies reported fatigue improvement with behavioural interventions
			Non-Significant R~~r~~esults:~~esults:~~ ~~Inconclusive effects with counselling due to poor methodological quality.~~No significant statistical data between counselling and the control group	
		Malcomson[3~~8~~]	**Significant Results:** 5 studies. 3 studies* found telephone administered CBT led to a significant reduction in depression (p= 0.02) (0.04), another study found depression levels were significantly reduced group using activity scheduling and cognitive techniques (p<0.01). A third study found CBT increased vitality (p=0.04). ~~Improvement in depression with CBT (p=0.004) but fatigue not an outcome measure.~~	
			Non-Significant R~~r~~esults: ~~None~~None.	
		Simpson[41~~40~~]	**Significant Results:** Effects of mindful breathing and movement in 3 studies* (n=187). One found significant improvements in fatigue at 3 and up to 6 months (MFIS. P=0.41) (MFIS. p=0.035). 2/3 studies had significant improvements in p values (p>0.05 and p=0.035).	
			Non-Significant R~~r~~esults: None	
		Asano[3~~5~~]	**Significant Results:** 2/4 studies* found significant improvement in fatigue 1=Mindfulness (ES=0.38), 2= CBT (ES=1.08, 2.99) and 1=relaxation (ES=1.79).	
			Non-Significant R~~r~~esults: ~~None~~2/4 studies found no significant improvement in fatigue.	
		Khan[3~~7~~]	**Significant Results:** None	
			Non-Significant R~~r~~esults: Inconclusive effects of tele-~~rehabiliation~~rehabilitation on fatigue due to the large bias (9 studies)	
		Plow[28]	**Significant Results:** 2 studies* found statistically significant improvements in depression with CBT. However, this data was not included.	
			Non-Significant Results: None	
Energy Conservation/Fatigue Management Interventions		Steultjens[40~~11~~]	**Significant Results:** ~~None~~1/2 studies* statistically significant decrease of impact of fatigue (effect size -0.75; 95% confidence interval -1.42 to 0.07). The other study found significant difference (0.01) on MSRF	**Significant Results:** 22~~/~~26/26~~29~~ studies reported improvement in MS fatigue with fatigue management interventions
			Non-Significant R~~r~~esults: ~~Inconclusive effects of ECT on fatigue due to limited evidence available.~~None	
		Thomas[10]	**Significant Results:** None	
			Non-Significant R~~r~~esults: Inconclusive effects on fatigue due to the small sample size of studies and not using fatigue as a primary outcome measure.	
		Lee[5]	**Significant Results:** 2 studies*. 1 study found significant positive results on MSRF (<0.01). The other study found significant positive effect on MSRF with energy conservation (p<0.01)~~None~~	
			Non-Significant results: ~~Inconclusive effects of ECT on fatigue due to limited evidence available~~None.	
		Plow[29~~8~~]*	**Significant Results:** 12 studies examined effects of fatigue management programs on fatigue. Statistical data was not included. Improvement in symptomatic fatigue reported.	
			Non-Significant results: None	
		Blikman[8]	**Significant Results:** 6 studies in total with 2 included in the meta-analysis. Meta-analysis concluded improvement in fatigue when ECT compared against no treatment (Fatigue Impact Scale (Cognitive: MD=2.91.95% CI), (Physical: MD=-2.99. 95% CI) and (Psychosocial: MD=-6.05. 95% Confidence Interval).	

			Non-Significant Results: None	
		Asano[365]	**Significant Results:** 4 ~~/8~~ studies had statistically significant results on fatigue with ECT (ES=0.53-0.84).	
			Non-Significant Results: None	
Multidisciplinary Interventions		Branas[354]	**Significant Results:** None	**Significant Results**: 3/~~66~~ studies reported improvement in MS fatigue with MDT interventions
			Non-Significant results: Inconclusive due to limited supporting evidence	
		Khan[380]	**Significant Results:** Significant improvement in disability with MDR (3 studies (n=217))	
			Non-Significant Results: Limited evidence for symptom improvement in OP and HR treatments (total of 2 studies n=302). Heterogeneous studies	
		Asano[365]	**Significant Results: None**	
			Non-Significant Results: Inconclusive due to the methodological quality and the limited effect size of 1~~the 2~~ study~~ies~~.	
Acupuncture		Karpatkin[376*]	**Significant Results:** 3 studies (n=7) but one study contained subjective qualitative reports of increase in energy levels. One study 25% of patients (n=20) had a decreased FSS score to below 30 after treatment. The mean reduction was 20.6 +-7.2. In the final study, the mean ODI score reduced pre and post treatment (pre: 41.16+-3.72)(post:33.59+-5.14).	**Significant Results:** Improvement on MS fatigue in one review. Note the review critiqued the poor methodological quality of the included studies
			Non-Significant Results: None	

Table 4 Non-pharmacological interventions and supporting evidence form review

*Note: * indicates review was deemed poor quality through critical appraisal process. Abbreviations. CFS=Chandler's fatigue scale, DFE= Diary of Fatigue Experience, ~~EDSS= Expanded Disability Status Scale,~~ FAI=Fatigue Assessment Instrument, FAMS=Functional Assessment of Multiple Sclerosis, FDI=Function and Disability Inventory, FIEDL= Fatigue Inventory of Effects on Daily Living, FIM= Functional Independence Measure, FIS=Fatigue Impact Scale, FSS=Fatigue Severity Scale, FSMC=Fatigue Scale for Motor and Cognitive Functions, HRQOL-MS=Health Related Quality of Life for Multiple Sclerosis, IPA, Impact on Participation and Autonomy, MAFS=Multidimensional Assessment of Fatigue Scale, MFI=Multidimensional Fatigue Inventory, MFIS=Modified Fatigue Impact Scale, MS-FS=Multiple Sclerosis Functional Score, MSQOL=Multiple Sclerosis Quality of Life, MSIS=Multiple Sclerosis Impact Scale, ODI= Oswestry disability index, POMS=Profile of Moods States, RIV= Rand Index of Vitality, SEP59=Multiple Sclerosis Quality Of Life scale, SF-36=Short Form-36 Vitality Subscale of the Short Form Health Survey, SIP=Sickness Impact Profile, SPFS=Subjective Perception of Fatigue Scale, VAS-Visual Analogue Scale. . *1-3 duplicate articles within findings, **4-6 duplicate articles within findings, *** 7+ articles*

Discussion

To the best of the author's knowledge this is the first review of reviews to consider and include the current review evidence. Given the synthesis and evidence from the results this review is able to make recommendations of the impact from specific pharmacological and non-pharmacological interventions on MSRF**.**

Clinical aim: to provide up-to-date evidence-based recommendations for the treatment of ~~MS related fatigue~~MSRF.

Scientific aim: To prioritise topics for future randomised clinical trials with sufficient power.

The c~~C~~riteria for ~~the~~ concluding/recommendation statements that related to the confidence of evidence ~~statements~~ combined the following factors; the methodological quality of reviews, evidence of risk of bias within supporting studies, and total number of studies (excluding duplications) supporting the research ~~and the number of supporting studies for the intervention.~~. Studies were rated as having no evidence to support a recommendation or were assigned one of three confidence related statements including: (1) '*w~~W~~ith ~~'~~caution'*(< 50% of studies had supporting evidence with 1 or less studies with high methodological quality), (2) '~~"~~*with moderate confidence'*~~"~~ (>50% of studies and 2 studies with high methodological quality) and (3) '~~"~~*with high confidence'*~~"~~ (>75% of studies and 3 or more studies with high methodological quality). ~~Considerations were made for the risk of bias, duplications and amount of current supporting studies.~~

Discussion of Pharmacological Evidence

No pharmacological studies contained strong evidence for their effectiveness in improving MSRF. Recommended for individual medications are examined below;

Amantadine

The guidelines for RCP[41~~2~~] and NICE[4] were examined. The NICE guidelines did not identify supporting evidence for its recommendation of amantadine and the RCP[42~~1~~]contained four RCTs, one randomised crossover trial and one CCT which supported the use of amantadine. Sixty-six percent of reviews included in this study (n=10/15) identified no significant improvement on MSRF. However, 6/11 studies were identified as duplicates and ~~a total of 6 duplications of studies from the reviews were included (11 studies in total).~~ t~~T~~he significant results from one study was included in 4 of the reviews. This lowers the power of the studies and accuracy of the results. Further, because of the high prevalence of side effects from Amantadine (20-60% of participants across studies) we have concluded that Amantadine should be considered "with caution". This conclusion is supported by a recent review that identifies no positive benefits from Amantadine on MSRF, however ~~current~~ this

evidence is underpowered and of a short duration[7]. Furthermore, another review[43] can only conclude amantadine has a modest effect on MSRF calling for larger clinical trials to support its recommendation in the NICE guidelines for MSRF.

Prokarin

The recommendation of Prokarin by the MS Society UK[42] however ~~the~~ to the best of the authors knowledge only one clinical trial~~s exists~~exist. Within the ~~current~~ existing evidence, only one review[5] identified a single study using Prokarin in MSRF. No duplications were found. A statistical improvement was identified but the study was underpowered and had methodological shortcomings. Given this ~~the current~~, the ~~-~~review is not able to give a recommendation relating Prokarin to MSRF ~~until further research is conducted~~.

Modafinil

A total of 7~~5~~1% (n=~~6~~5/~~8~~7) of studies in ~~two~~ three reviews[5,27~~8~~,36] found significant improvements in MSRF. Only two duplications were found between reviews (7 studies in total). However, another review[43] found weak evidence supporting the use of Modafinil in MSRF and the NICE guidelines do not currently support the use of this drug for MSRF. Thus, the current review can recommend Modafinil with "caution" but calls for larger clinical studies to be conducted.

Other medications not currently recommended

Six drugs (Pemoline, Carnitine, Aspirin, Aminopyridine, 3,4 Diaminopyridine, Interferon Beta 1b) and anti-depressants were considered.

Pemoline

The RCP[4~~1~~2] recommends Pemoline for MSRF management, however Tur[7] identifies negative results and notes the withdrawal of the drug for other conditions. We identified that 75% (n=3/4) of studies found Pemoline had no significant effect on MSRF in 2 reviews[3~~5~~4,5]. However there was a duplication between the reviews reducing the power of the results (3 studies in total). Thus, the current evidence ~~we~~ suggests the evidence should be considered 'with caution' that Pemoline has limited or no effect on MSRF. ~~with "some confidencewith caution" that Pemoline has limited or no effect on MSRF.~~

Carnitine

Tejani[2~~65~~,2~~67~~ ~~were inconclusivehad~~identified insignificant results o~~i~~n the effect of carnitine on MSRF with 1 duplication found between reviews. ~~,~~ Tur[7] found 2 experimental studies that identified some beneficial effect however, due to ~~the~~ both studies ~~being underpowered~~ having a small sample size thus reducing its power and a lack of a placebo in one. Tejani [27] concluded that the use of carnitine in clinical practice cannot be recommended as its effects on fatigue is unknown. ~~f~~Further ~~-~~research ~~i~~in this area cannot be advised due to a lack of supporting evidence.~~s required.~~ We cannot recommend Carnitine currently due to no supporting evidence.

Medications with little or no supporting evidence

Only one study in a past review[5] considered Aspirin, this study identified a significant improvement on MSRF, however due to the limited evidence no recommendation can be made. Currently there are no reviews available to discuss the effectiveness of Aminopyridine, 3,4 Diaminopyridine, Interferon Beta 1b and antidepressants in MSRF management.

Discussion of Non-P~~p~~harmacological Evidence

The recommended interventions are discussed below;

~~*Education*~~*Energy Conservation and Fatigue Management Programs*

~~Tur[7] along with NICE guidelines[4] also recommend education programs for MSRF.~~ The current review identified a total of ~~76~~100%26 ~~(n=19/22)~~ studies across 6 reviews found an improvement in MSRF with either ~~energy conservation or fatigue management~~ program~~s~~. Nevertheless, duplications of studies were found resulting in only 14 studies. On the other hand, two systematic reviews[7,43] along with NICE guidelines[4] also recommend energy conservation or fatigue management programs for MSRF. ~~Thus~~Thus, both programs are recommended with ‘‘~~“~~high confidence’’~~”~~ as effective for management of MSRF.

Multidisciplinary (MDT) Interventions

MDT interventions are recommended by NICE guidelines[4] involving both physical and psychological treatments. Other review evidence[7,43~~4~~] identified improvements from complex interventions involving several techniques like exercise and energy effectiveness techniques. A total of 50% (n=3/~~6~~6) of studies found a significant improvement in MSRF. Given this it is stated ‘with ‘‘~~“~~caution’’~~”~~ that MDT interventions may be beneficial in fatigue improvement.

Psycho-behavioural interventions

CBT and mindfulness are recommended by NICE guidelines[4] for MSRF management. This is supported by other review evidence[44~~3~~5]. A meta-analysis of one review[46] found CBT interventions were more superior in reducing fatigue severity (-0.60:95% CI) compared to non-CBT interventions (-0.20: 95% CI). ~~Only~~ However, in this review of reviews; ~~27~~45% (n=~~5/18~~10/22) of studies found a significant improvement on fatigue with psycho-behavioural interventions. However, duplications of these studies were found giving a total of 11 studies affecting the accuracy of this data. A meta-analysis by Van den Akker[46] found a moderately positive short-term effect with CBT in MSRF. Given this we recommend generic psycho-behavioural interventions ‘with ‘‘~~caution~~moderate confidence’’~~”~~. ~~F~~Further research with higher quality studies should be conducted ~~in order to~~to investigate the potentially positive effects of CBT.~~,~~

Exercise interventions

~~A large number of~~Many reviews grouped exercise interventions together and concluded that exercise can improve MSRF[40]. However, specific conclusions around the type of exercise is required if results are to be used in clinical practice.

Endurance training (increase in endurance to sustain exercise for a greater duration) is ~~currently~~ not recommended in NICE guidelines[4] and Tur[7] did not discuss the endurance training. A total of 51~~7~~9% (n=19/3~~7~~4) of studies concluded that endurance training has a significant improvement on MSRF. There were 9 duplications of different studies (23 studies in total) -This is stated ‘‘~~“~~with ~~high~~ moderate confidence’’~~”~~.

Aerobic training is ~~currently~~ recommended by NICE guidelines[4]. Other review evidence[7,35~~4~~] has identified some confusion into its effects. ~~However, a~~A total of 6~~8~~0% (n=11~~6~~/16~~0~~) of studies in three reviews found aerobic training (changes in aerobic and cardiovascular capacity) had some benefit on MSRF which we state ‘with ‘‘~~“~~moderate~~some~~ confidence’’~~”~~. However,~~—~~ overlapping definitions to endurance exercise meaning terms used by reviews may influenced the studies obtained and conclusions given~~).~~ In addition, 14 studies excluding duplicates (n=4) were used in total affecting the overall power of the results. ~~had some benefit on MSRF which we state with “some confidence”.~~

Comment [AS6]: needed

Comment [AS7]: don’t need this – not sure what it gives

Comment [PM8]: This was the review as

Yoga is recommended in NICE guidelines[4] along with the MS Society UK[4~~22~~]. A total of 81% of studies (n=18/22) found yoga to have a significant improvement on MSRF. However,~~However, it must be noted that~~ there were 7 duplications of one study and there were 9 studies in total. Taking the NICE guidel~~ that~~ ines into consideration, this statement is made '~~concluded~~ with "~~high~~ moderate confidence'"~~~~.

The NICE guidelines[4] recommend progressive resistance training in a combined physical and behavioural program. ~~Current~~ Existing review evidence supports[7] this. 14 studies excluding duplicates (n=5) were used in total. A total of 68~~53~~% (n=13~~16~~/19~~30~~) of studies found a significant improvement on MSRF with resistance training in 4 reviews ~~-~~and considering the NICE guidelines the results are ~~that is~~ stated 'with "~~some~~moderate confidence'"~~~~.

Comment [AS9]: how many

A combination of exercise/combined training is recommended in NICE guidelines[4]. Only 3 duplications of studies were found. A total of ~~52~~87% (n=20~~13~~/2~~35~~) of studies found that combined training had a significant improvement on MSRF in 5 reviews which is stated 'with "~~some~~ high confidence'"~~~~. It must be acknowledged that the combined training was different in each study and therefore large powered randomised studies with similar interventions should be examined to find the most effective intervention~~ in combined training~~. Considering the heterogeneity of the data we ~~state~~consider 'with some confidence' that combined training ~~ that this intervention~~ positively affects ~~fatigue~~MSRF. ~~with "some confidence" due the heterogeneity of the interventions~~

~~*Currently not recommended*~~ *Interventions not Currently Recommended*

Acupuncture

Karpatkin[3~~76~~] found significant improvements in MSRF with acupuncture treatment. This is stated '~~"~~with caution'"~~~~ as the review was poorly conducted ~~and the~~and the included studies were of poor quality.

Clinical Implications

Below we detail evidence 'with "high confidence'"~~~~ of a beneficial effect on MSRF:

Pharmacological Interventions

At present, ~~T~~there is ~~currently~~ no single drug that we would recommend. Considering the NICE guidelines, Amantadine is the only pharmacological treatment that is used in clinical practice for MSRF~~MSRF and therefore is continued to be used at present~~. However, the evidence to support its use is not strong. New RCTs to support its positive effects on ~~fatigue~~MSRF should be conducted.~~and~~ F~~f~~urther research into the potential positive effects on Modafinil is ~~needed~~warranted.

Non-Pharmacological Interventions

Education is recommended as an effective treatment for MSRF.

Recent evidence[44] has identified the following education is required: (1) others- including ~~(~~health care professionals, carers or family members~~)~~ need to be educated about MSRF and be careful not to consider MSRF as equivalent to their own experiences fatigue, (2) patients would benefit from understanding and accepting the impact of MSRF (3) patients should be supported to plan activities of daily living and rest periods that can accommodate the MSRF.

~~Endurance training and~~ Yoga interventions have supporting evidence that allow us to recommend these interventions in MSRF treatment.

~~Current c~~Clinical guidelines for Yoga include:

The evidence identified from this review suggests that Yoga ~~was found in this review of reviews to have~~ likely has a significant improvement on MSRF which is in ~~correlation~~ agreement the past NICE[4] guidelines which recommends Yoga for MSRF. ~~with NICE guidelines[4] in which 'aerobic, balance and stretching exercises including yoga' are recommended.~~ The prescription of Yoga should include the following parameters:

Frequency: 1-3 times per week (average 1)[5,3~~4~~3,2,3~~2~~1,3~~2~~3,30~~29~~,3~~6~~5

Time: 60-90 mins[5,3~~4~~3,2,3~~1~~2,3~~2~~3,30~~29~~,3~~6~~5

Type: Iyengar[5,2,3~~1~~2,3~~2~~3,30~~29~~,3~~5~~6, Hatha[3~~1~~2, 3~~3~~2, Unspecified[5,3~~2~~1,3~~2~~3,~~29~~30,3~~5~~6, Tai-chi[3~~2~~3

Current clinical guidelines[9,29,32,34] for endurance training include:

The evidence from this review suggested that endurance training improved MSRF, this ~~is in agreement~~agrees with NICE[4] guidelines. The prescription of endurance training should include the following parameters ~~building up sessions towards the following parameters~~ (where studies are not reference no detail was given):

Frequency: 2-5 days per week[9,3~~2~~3,3~~4~~5

Intensity: average percent of maximum heart rate during aerobic exercise 40-85% of HR[9,30~~29~~

Time: 30 minutes per session[9,30~~29~~

Type of exercise: walking[9,3~~2~~3,~~29~~30, ergometric cycling [9,30~~29~~, cycling[3~~3~~2, endurance type training devices[3~~3~~2, lower limb endurance exercises[3~~5~~4, circuits[30~~29~~ and upper body ergometry[~~29~~30.

Limitations

The following limitations are acknowledged: Most included participants had moderate to severe fatigue, thus findings may be most applicable to this group. The participants' diagnosis was not listed in every review, thus the application of results to sub-types of MS is not possible. In addition, the gender most often was identified as female or unknown. Asano[25] reported ~~varying effects of interventions on different~~ diagnosis, age and gender as covariates that impacted on the effectiveness of the intervention for ~~in~~ MSRF. The current results don't consider the impact of these covariates. ~~These factors will therefore impact the results found in the reviews of reviews.~~

The inclusion criteria of the reviews were not always clear and therefore some inaccuracies in the data should be acknowledged. Furthermore, some interventions studied in this review of reviews were not designed to treat ~~fatigue~~MSRF~~, or have a primary outcome measure related to~~ MSRF~~.~~ ~~and thus not being a primary outcome on which studies were conducted.~~ This affects the specificity of the data and the accuracy of the conclusions made on interventions not primarily measuring MSRF.

~~-~~Due to a lack of randomised control trials forms of bias likely influence and limit the internal or external validity of the results. ~~Considering randomised controlled trials are criterion for efficacy and effectiveness of studies the importance of new studies~~Further adequately powered ~~being~~ RCTs are needed to ~~have~~generate the most accurate and reliable data on which to base conclusions. ~~-~~The results may be limited by the synthesis techniques undertaken. The number of outcome measures along with poor psychometric properties may compromise the findings by limiting the ability of this review to

Comment [AS10]: did they say 1 paragraph or leave as is? If no comment leave as is

Comment [AS11]: you say this at the end of paragraph 3 keep in?

identify benefits by domain of MSRF. Furthermore, the included reviews contained studies that did not have fatigue as a primary outcome measure and therefore the interventions on MSRF may not be accurate creating false-positive and false negative results leading to misinterpretation of the data.

Duplications of the articles across reviews were included. This could lead to a misrepresentation of the data. However, including the summaries of the data, there is still information that can be gathered from this review of reviews.

Conclusion

This current review of reviews has been able to recommend the use of education (energy conservation and fatigue management) and~~,~~ yoga ~~and endurance training~~ as effective interventions for MSRF. Combined training was found to have strong evidence supporting its use in MSRF. However, the studies had dissimilar interventions and therefore the recommendation for combined training on this review cannot be made. Overall, ~~T~~these recommendations are limited by data heterogeneity and specificity of the included outcome measures in studies to MSRF. We recommend further well-powered RCTs with the following promising fatigue interventions: (1) for the pharmacological treatments of MSRF consideration to Amantadine and Modafinil and (2) for the non-pharmacological treatment of MSRF ~~the non-pharmacological treatment of~~consideration to CBT and subtypes of exercise training. ~~We recommend that further interventions be conducted.~~

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