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Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease (Review)

Gibbons C, Pagnini F, Friede T, Young CA

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[Intervention Review]

Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease

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ABSTRACT

Background

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is terminal, progressive neurological condition for which there are no curative treatments. Among people with ALS/MND, fatigue is a common and debilitating symptom, which is characterised by reversible motor weakness and whole-body tiredness that is only partially relieved by rest. The effectiveness of pharmacological or non-pharmacological treatments for fatigue in ALS/MND is not yet established.

Objectives

To assess the effects of pharmacological and non-pharmacological interventions for fatigue in ALS/MND.

Search methods

We searched the following databases on 5 September 2017: Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL Plus, and ERIC. We also searched two clinical trials registries.

Selection criteria

We selected randomised and quasi-randomised controlled trials of any intervention which sought to reduce fatigue for people with ALS/MND. We included studies if reduction in fatigue was a primary or secondary outcome of the trial.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

We included one pharmacological (modafinil) study and three non-pharmacological studies (resistance exercise, respiratory exercise, and repetitive transcranial magnetic stimulation (rTMS)), involving a total of 86 participants with ALS/MND. None of the included studies were free from risk of bias. Since there was only one trial for each intervention, no meta-analysis was possible. All studies assessed fatigue using the Fatigue Severity Scale (FSS; scale from 9 to 63, higher scores indicate more fatigue). Information for assessing bias was often lacking in study reports, making the risk of bias unclear across several domains in all trials. Blinding of participants was not possible in exercise trials, but the outcome assessment was blinded.

We found very low-quality evidence suggesting possible improvements in fatigue for modafinil treatment versus placebo (MD -11.00, 95% CI -23.08 to 1.08), respiratory exercise versus a sham intervention (MD -9.65, 95% CI -22.04 to 2.73), and rTMS versus sham rTMS (data not provided), which warrant further investigation to clarify the efficacy of these treatments for fatigue in ALS/MND. We found no clear improvements in fatigue for resistance exercise versus usual care (MD 0.20, 95% CI -10.98 to 11.38; very low-quality evidence).

Three participants in the modafinil group dropped out of the modafinil study, two citing issues with headache and one with chest tightness; other adverse effects were anxiety, nausea, dizziness, and sialorrhoea (probably ALS-related). The trials reported no adverse effects of exercise or rTMS.

We cannot be certain about the effects of any of the interventions studied because of imprecision (small numbers of participants, wide CI), and possible study limitations.

Authors' conclusions

It is impossible to draw firm conclusions about the effectiveness of interventions to improve fatigue for people with ALS/MND as there are few randomised studies, and the quality of available evidence is very low.

PLAIN LANGUAGE SUMMARY

Treatments for extreme tiredness and lack of energy (fatigue) in amyotrophic lateral sclerosis/motor neuron disease

Review question

What are the effects of treatments for fatigue in people living with amyotrophic lateral sclerosis (ALS) compared to no treatment or placebo?

Background

ALS, which is also known as motor neuron disease (MND), is a condition in which the nerves that control movement stop working. People experience problems moving their limbs, maintaining posture, swallowing, and breathing, which worsen over time and shorten life. The cause is unknown, and there is no cure. People living with ALS/MND often experience fatigue, which can cause distress and reduce quality of life. Fatigue can have many causes, including respiratory problems, medication, malnutrition, and depression. Our focus in this review was on treatments for fatigue that arises from the condition itself. Different treatments may improve symptoms of fatigue in ALS/MND. These include medicines, which may help people feel more awake, and other treatments, such as exercise. It is unclear whether any of these treatments are effective for improving fatigue in ALS/MND. We reviewed the available studies on the effects of treatments for fatigue in ALS/MND.

Study characteristics

The review included four small studies with a total of 86 participants. Each study investigated a different treatment. These were a drug treatment (modafinil) compared to placebo, breathing exercises compared to sham (inactive) breathing exercises, exercises with weights compared to usual care, and magnetic brain stimulation compared to sham rTMS.

Key results and quality of the evidence

We are very uncertain about the effects of modafinil, breathing exercises, exercises with weights, or magnetic brain stimulation on fatigue in people with ALS/MND, as the evidence was very low quality. It was often unclear whether studies were adequately designed and performed, as trial reports often lacked details. The results of these small studies were not precise. Three participants stopped taking modafinil because of side effects: headache in two, and chest tightness in one; participants also reported anxiety, nausea, dizziness, and sialorrhoea (inability to control oral secretions). We need more research on effective treatments for fatigue in ALS/MND.

The searches are up to date to September 2017.

Summary of findings for the main comparison. Modafinil compared to placebo in ALS/MND

Modafinil compared to placebo in ALS/MND						
Patient or population: people with ALS/MND **Setting:** Eleanor and Lou Gehrig MND/ALS Research Centre **Intervention:** modafinil **Comparison:** placebo						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with modafinil**				
Fatigue assessed with: Fatigue Severity Scale (FSS) Scale from: 9 to 63 (higher indicates more fatigue) follow up: 4 weeks	The mean FSS score was 43	MD 11 lower (23.08 lower to 1.08 higher)	-	32 (1 RCT)	⊕⊖⊖⊖ Very low[1]	
Adverse events	Three adverse events led to discontinuation of modafinil (2 headache, 1 chest tightness). Anxiety (in 2 people), nausea (in 2), dizziness (in 1), and sialorrhoea (in 1; probably ALS-related) also occurred with modafinil. Placebo group adverse events were not reported - it is not clear whether there were none.		-	32 (1 RCT)	⊕⊖⊖⊖ Very low[2]	The trial reported the number of adverse events in the treatment group, but not numbers of events in the placebo group or number of people experiencing adverse events

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the quality of evidence 3 times: once for study limitations and twice for imprecision. The security of blinding in the trial was unclear and the report did not provide enough information to assess attrition and selective reporting. The trial was small and the CI of the effect estimate included appreciable benefit and little or no effect.
[2]We downgraded the quality of evidence 3 times: once for study limitations, twice for imprecision. Reporting of adverse events was incomplete and security of blinding unclear. The trial was small and the event rate low.

Summary of findings 2. Exercise compared to usual care in ALS/MND

Exercise compared to usual care in ALS/MND

Patient or population: people with ALS/MND
Setting: physical therapy service
Intervention: exercise
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with usual care	Risk with exercise				
Fatigue assessed with: Fatigue Severity Scale (FSS) Scale from: 9 to 63 (higher indicates more fatigue) follow up: 6 months	The mean FSS score was 42.7	MD 0.2 higher (10.98 lower to 11.38 higher)	-	18 (1 RCT)	⊕⊖⊖⊖ Very low[1]	-
Adverse events	No adverse events were reported		-	18 (1 RCT)	⊕⊖⊖⊖ Very low[1]	None of the people who discontinued did so because they thought the exercise programme was making their condition worse. No participants reported excessive soreness, cramping, or fatigue.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the evidence 3 times to low quality: twice for imprecision as the trial was very small and CI included appreciable benefit and appreciable harm. The third downgrading was for study limitations as the nature of the intervention prevented participant blinding.

Summary of findings 3. Inspiratory muscle training compared to sham intervention in ALS/MND

Inspiratory muscle training compared to sham intervention in ALS/MND

Patient or population: people with ALS/MND
Setting: home-based intervention
Intervention: inspiratory muscle training
Comparison: sham intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk or value with sham intervention	Risk or value with inspiratory muscle training				
Fatigue assessed with: Fatigue Severity Scale (FSS) Scale from: 9 to 63 (higher indicates more fatigue) follow up: 4 months	An illustrative mean FSS score in the absence of inspiratory muscle training is 42.7[1]	MD 9.654 lower (22.04 lower to 2.73 higher)	-	24 (1 RCT)	⊕⊖⊖⊖ Very low[2]	
Adverse events	The trialists stated that the exercise protocol had no adverse effects.		-	24 (1 RCT)	⊕⊖⊖⊖ Very low[2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]The mean FSS score in the control group after 4 months was not available from Pinto 2012. The value given here, for illustrative purposes, is the control group mean at 6 months from Dal Bello Haas 2007.
[2]We downgraded the quality of evidence 3 times to very low: twice for imprecision and once for study limitations. The trial was very small and CI included appreciable benefit and little or no effect. The nature of the intervention meant that the trainer was aware of the intervention group.

Summary of findings 4. Repetitive transcranial magnetic stimulation (rTMS) compared to sham intervention in ALS/MND

Repetitive transcranial magnetic stimulation (rTMS) compared to sham intervention in ALS/MND

Patient or population: people with ALS/MND
Setting: secondary care
Intervention: repetitive transcranial magnetic stimulation (rTMS)
Comparison: sham intervention

Outcomes	Impact	Number of participants (studies)	Quality of the evidence (GRADE)
Fatigue assessed with: Fatigue Severity Scale (FSS) follow-up: 2 weeks	No FSS scores were given. The investigators assessed fatigue with the FSS using 2-way analysis of variance (within-subjects factor time, between-subjects treatment arm). The trial reported a significant effect for fatigue at the end of the follow-up period. The effect was non-significant following post hoc Bonferroni adjustments (data not reported).	10 (1 RCT)	⊕⊖⊖⊖ Very low[1]
Adverse events	No adverse events were reported.	10 (1 RCT)	⊕⊖⊖⊖ Very low[1]

RCT: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the quality of evidence 3 times: once for study limitations and twice for imprecision. The risk of bias was unclear as the trial report provided too little detail for assessment. The trial involved 10 people.

BACKGROUND

Fatigue is a commonly reported symptom in people with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) (Ramirez 2008), with a large proportion of people reporting 'clinically significant' levels of fatigue (McElhiney 2009). Fatigue in ALS/MND has been defined as "reversible motor weakness and whole-body tiredness that was predominantly brought on by muscular exertion and was partially relieved by rest" (Gibbons 2013a). In ALS/MND, fatigue is distinguished from sleepiness by feelings of weariness or exhaustion that do not necessarily beget a desire to sleep. This fatigue appears to be experienced predominantly as general (feelings of whole-body tiredness) and physical (reversible motor weakness). People with other neurological diseases, such as multiple sclerosis, describe an experience of general physical fatigue occurring alongside cognitive fatigue (reversible reduction in concentration or mental performance)(Lou 2003; Mills 2008).

In ALS/MND, fatigue can be experienced as a pervasive feeling of tiredness or lethargy, or as an objective decline in the ability of a muscle to contract to maximum force (Gibbons 2011; Lou 2012). The first type of fatigue is ubiquitous in humans, and may have been experienced by the individual before diagnosis; however, following development of ALS/MND, the severity of this fatigue and precipitating factors substantially change. The second type of fatigue, objective motor fatigue, also known as physical fatigability, is unique to the disease state and is not normally within a person's previous experience. Both types of fatigue have been shown to be important to people with ALS/MND (Gibbons 2011), and fatigue, more generally, impacts negatively upon quality of life (Lou 2003).

Evidence for the relationship between fatigue and functional ability is conflicting. Although some studies have suggested that fatigue is related to functional capacity (Lo Coco 2012; McElhiney 2009), others have been unable to support this claim (Gibbons 2011; Ramirez 2008). Fatigue appears to be related to common nighttime complaints in ALS/MND, including muscle cramps and nocturia (Lo Coco 2012). Fatigue is related to psychological distress, social withdrawal, and reduced quality of life for people with ALS/MND (Gibbons 2013b; Lou 2003).

Description of the condition

ALS/MND is a progressive, terminal neurodegenerative disease of unknown aetiology that is currently without a cure. The incidence of ALS/MND is around 2.16 per 100,000 person-years (Logroscino 2010). At any one time, approximately 5000 people in the United Kingdom are affected (Shaw 1999), and 25,000 in North America (McGuire 1996).

Rapid progression of the disease causes weakness and muscular atrophy, impacting upon an individual's ability to carry out activities of daily living, such as dressing, bathing, and eating. Problems with speech and swallowing often occur as the result of weakness in bulbar musculature. As the disease progresses, breathing issues (including nocturnal hypoventilation and reduced sleep quality) become apparent, and may progress until respiratory failure occurs (Bourke 2004). Death has been reported in most people with MND within two to five years following diagnosis, usually from respiratory failure, caused by respiratory muscle weakness (Rowland 2001).

Description of the intervention

Currently, no evidence-based treatment is available for fatigue in people with ALS/MND. Several drugs have been investigated as treatment for fatigue in this population, including amantadine, pemoline, and bupropion, although evidence regarding their efficacy is lacking (Jackson 2006). Modafinil, a novel wakefulness-promoting agent that has been approved for the treatment of excessive sleepiness associated with narcolepsy, may also be an effective treatment for fatigue (Carter 2005; McElhiney 2009; Rabkin 2009).

Dietary supplementation of creatine may increase, or at least preserve, muscular strength, and reduce levels of fatigue (Rosenfeld 2008).

Other non-pharmacological therapies may be used to ameliorate fatigue. Studies have evaluated the potential benefits of supported treadmill ambulation (Sanjak 2010), muscular exercise (Drory 2001), and repetitive transcranial magnetic stimulation (rTMS) (Guo 2012; Zanette 2008) for this purpose.

How the intervention might work

Pharmacological interventions that stimulate the central nervous system (CNS) may reduce generalised fatigue for people with ALS/MND. Modafinil stimulates the release of norepinephrine and dopamine from synaptic terminals and elevates hypothalamic levels of histamine (Ishizuka 2008). Creatine, which increases maximum availability for energy output in anaerobic activities, may also have a positive effect on muscle strength and fatigue (Ellis 2004; Kley 2013; Rosenfeld 2008). Different treatments may be effective for different forms of fatigue.

Non-pharmacological interventions may focus on light exercise, including supported or unsupported exercises (e.g. walking), or resistance training using weights (Bello-Haas 2007).

Why it is important to do this review

Fatigue is prevalent in people with ALS/MND and has a significant impact on quality of life. Presently, clarity regarding the best management of fatigue in this population is lacking. This review is the first systematic review of pharmacological and non-pharmacological interventions for fatigue in ALS/MND. The purpose of this review is to identify interventions to reduce primary fatigue, which is disease related. We will not consider secondary causes of fatigue, such as malnutrition and chronic respiratory failure, which have been assessed in other Cochrane systematic reviews (Katzberg 2011; Radunovic 2017).

OBJECTIVES

To assess the effects of pharmacological and non-pharmacological interventions for fatigue in ALS/MND.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised controlled trials, which assessed the effectiveness of pharmacological and non-

pharmacological treatments for fatigue in people with ALS/MND in this review.

Types of participants

We included studies in which study participants were diagnosed with possible, probable, or definite ALS/MND, according to recognised criteria, preferably the El Escorial criteria (Brooks 2000).

Types of interventions

We included all interventions that aimed to reduce fatigue in people with ALS/MND, and measured it as either a primary or a secondary objective. These pharmacological or non-pharmacological treatments could be compared to each other, placebo, or standard care. Examples of such treatments included drug treatments (e.g. modafinil) and behavioural interventions.

Types of outcome measures

Primary outcomes

The primary outcome was level of fatigue at the end of the follow-up period.

Fatigue could be evaluated using any validated patient- or clinician-administered fatigue questionnaire that measures general fatigue, including the Modified Fatigue Impact Scale (MFIS) (Fisk 1994) and the Fatigue Severity Scale (FSS) (Krupp 1989). We also included questionnaires that measured general fatigue and reversible muscle weakness, such as the Neurological Fatigue Index–MND (NFI-MND) (Gibbons 2011).

Secondary outcomes

Secondary outcomes were assessed at the end of the follow-up period, and could include the following.

1. Sleepiness of participants measured by a validated scale including the Epworth Sleepiness Scale (ESS) (Johns 1991).
2. Depression measured by a validated scale or by a clinical diagnostic interview, including the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983), or the Beck Depression Inventory (BDI) (Beck 1988).
3. Quality of life of participants measured by a validated objective or subjective instrument, including the ALS Specific Quality of Life-Revised (ALSSQOL-R) (Felgoise 2008), the McGill Quality of Life Questionnaire (Cohen 1995), or the Short Form-36 Health Survey (SF-36) (Ware 1992).
4. Functional status of participants measured by a validated scale such as the ALS Functional Rating Scale-Revised (ALSFRS-R) (Cedarbaum 1999).
5. Adverse effects.

Search methods for identification of studies

Electronic searches

We searched the following databases on 5 September 2017.

- Cochrane Neuromuscular Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web); (searched 5 September 2017) using the search strategy in Appendix 1
- MEDLINE (1966 to August 2017) using the search strategy in Appendix 2.
- Embase (1980 to August 2017) using the search strategy in Appendix 3.
- PsycINFO (1806 to August 2017) using the search strategy in Appendix 4.
- CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature Plus; 1937 to August 2017) using the search strategy in Appendix 5.
- ERIC (1966 to August 2017) using the search strategy in Appendix 6

Searching other resources

We scanned available conference abstracts from International ALS/MND Symposia for relevant studies. We checked all references in the identified trials, and contacted trial authors to identify additional published or unpublished data. We searched trial registries (US National Institutes of Health trials registry, ClinicalTrials.gov (clinicaltrials.gov/), and the World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/)) to identify ongoing trials. We considered trials published in languages other than English to be eligible for inclusion, following translation.

Data collection and analysis

Selection of studies

Three review authors (CAY, CG, and FP) checked titles and abstracts identified during the electronic searches. These review authors obtained the full text of all potentially relevant studies for independent assessment. All review authors independently assessed which trials fit the inclusion criteria. We resolved disagreements about inclusion criteria by discussion and consensus.

We excluded duplicate reports, and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (CG and FP) independently extracted data onto a specially designed form; the other two review authors (CAY and TF) checked the data extraction. One review author entered the data into the software (CG), another (FP) checked the entered data.

Where data allowed, we extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study settings, withdrawals, and date of study.
2. Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Assessment of risk of bias in included studies

Two review authors (CG and FP) independently assessed risk of bias for each study using the Cochrane 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). All review authors discussed disagreements related to risk of bias, and reached a consensus. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other sources of bias.

We graded studies as having high, low, or unclear risk of bias in each of these domains, and provided justifications for these judgements in the 'Risk of bias' table in Characteristics of included studies.

Measures of treatment effect

If sufficient studies had been included, we would have evaluated treatment effects for continuous outcomes using mean differences (MDs), or standardised mean differences (SMDs) for results across studies with outcomes that were conceptually the same, but measured in different ways. In the event that studies presented dichotomous data (e.g. responder analyses), we would have used risk ratios (RRs). We would have calculated 95% confidence intervals (CIs) for the measures of treatment effect.

We would have undertaken meta-analyses only where meaningful, that is, when treatments, participants, and the underlying clinical questions were similar enough for pooling to make sense.

Assessment of reporting biases

If we had identified a large number of eligible studies, we would have analysed a funnel plot to assess the potential existence of small-study bias.

Data synthesis

We had planned to use the random-effects model for the summary effect measure in any meta-analysis. The weights for the studies would have been be inverse to the variances. The random-effects model incorporates possible between-study variation as well as within-study differences, and so is more conservative. The fixed-effect model assumes that no between-study differences exist. Both models yield very similar results, unless significant between-study differences are noted (heterogeneity).

'Summary of findings' table

We created 'Summary of findings' tables, using fatigue as the outcome. We used the five GRADE considerations (study limitations, inconsistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contributed data for the outcome). We also included adverse events. Since we included only RCTs and quasi-RCTs in this review, we started from an assumption of high-quality evidence, from which we downgraded the quality to moderate, low, or very low, based on the extent to which the GRADE considerations presented a threat to validity. We used methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011) and GRADEpro software (GRADEpro 2008). We justified all decisions to downgrade or upgrade the quality of studies using footnotes, with comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We would have assessed the level of functional impairment, measured using the ALSFRS-R (Cedarbaum 1999), to identify heterogeneity of participants. If numbers had allowed, we would have used this scale to create subgroups of participants to analyse separately and compare.

Sensitivity analysis

If a study was of doubtful eligibility for the systematic review, appeared to be an outlier, or had missing data that were impossible to retrieve, we had intended to compare the results of analyses with and without the trial. However, there was only one trial for any comparison.

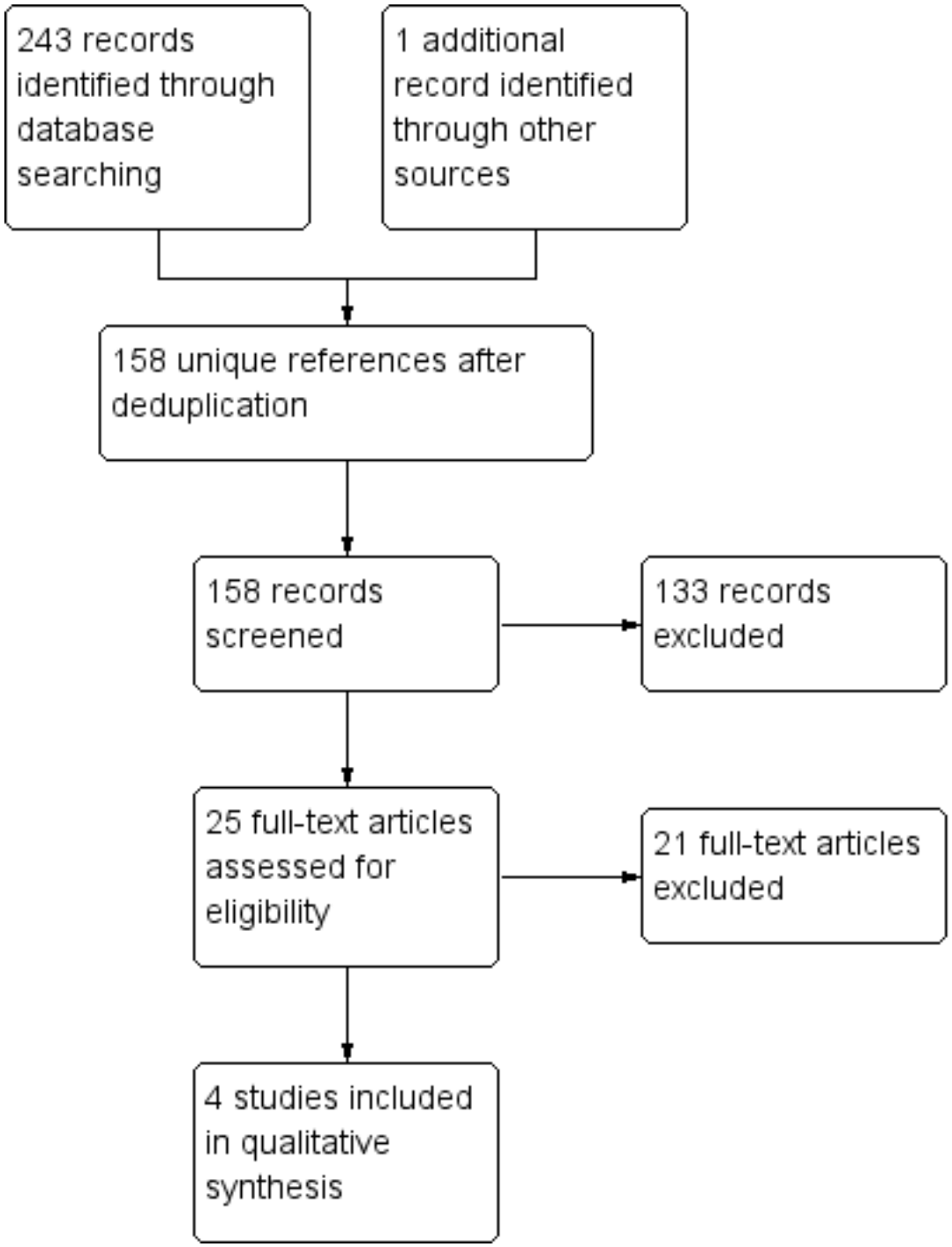
This review has a published protocol (Gibbons 2014).

RESULTS

Description of studies

Our searches identified a total of 243 reports. After we removed duplicates, we had 157, 25 of which were potentially relevant randomised controlled trials (RCT). The number of references returned from each database was: Cochrane Neuromuscular Specialised Register 31, CENTRAL 52, MEDLINE 56, Embase 80, PsycINFO 3, CINAHL Plus 20, and ERIC 1. We identified one additional reference from other sources. See Figure 1 for a PRISMA flow chart illustrating the study selection process.

Figure 1. Study flow diagram



Included studies

Modafinil versus placebo

The double-blind trial by Rabkin and colleagues aimed to evaluate the effect of modafinil on fatigue in people with probable or definite ALS by modified El Escorial criteria (Rabkin 2009). They used a 3:1 modafinil:placebo design, in doses up to 300 mg/day for four weeks, followed by eight weeks of open maintenance treatment. Measures were collected at baseline, weeks two and four, and biweekly thereafter. Primary outcome analyses were conducted at week four. The primary outcome was fatigue, measured by the FSS. Secondary outcomes included sleepiness and depression.

Resistance exercise versus usual care

Dal Bello Haas and colleagues conducted a RCT of resistance exercise for people with clinically definite, probable, or laboratory-supported amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) (Dal Bello Haas 2007). Twenty-seven participants were randomly assigned to either a resistance exercise group (N = 13), or a usual care group, which consisted of stretching exercises (N = 14).

Participants in the resistance exercise group were given stretching exercises plus an individualised moderate-load and moderate-intensity resistance exercise programme for upper and lower limbs. Participants were assessed at baseline, and once monthly for six months thereafter. The primary outcome of the study was change in global function, measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS). Secondary outcomes were health-related quality of life (measured using the Short Form 36 (SF-36) Health Survey), and fatigue (measured using the Fatigue Severity Scale (FSS)).

Respiratory exercise versus sham intervention

This study evaluated the effect of respiratory exercise in people with definite or probable ALS (Pinto 2012). The intervention was inspiratory muscular training, consisting of inhaling and exhaling through a threshold-inspiratory muscle training (IMT) device, which was a plastic cylinder with a mouthpiece and spring-loaded valve that could be set to different pressure thresholds. Twenty-six participants were recruited into the trial; all participants received an IMT device. The participants were randomised into either an active intervention group (IMT resistance set at 30% to 40% of maximal inspiratory pressure (MIP)) or a sham intervention group (IMT resistance set to the lowest possible load, to remove any therapeutic effect). All participants received instructions to blow into the tube for 10 minutes twice daily. After an initial four-month intervention period, all participants received the active intervention for a further four months. The primary outcome measure was decline in ALSFRS. Other outcomes relevant to this review were the respiratory subscore of the ALSFRS; fatigue assessed using the FSS, depression (Hamilton Rating Scale for Depression (HRSD)), sleepiness (Epworth Daytime Sleepiness Scale (ESS)), the Functional Independent Measure (FIM), which is an 18-item ordinal scale of independence, and quality of life (measured using the EuroQol-5D). Trialists evaluated fatigue during respiratory training by the Borg scale.

Repetitive transcranial magnetic stimulation (rTMS) versus sham intervention

Zanette and colleagues conducted a randomised-controlled pilot study to assess the effect of 5-Hz repetitive rTMS on motor performance, fatigue, and quality of life (QoL) (Zanette 2008). Ten people with probable or definite ALS attended a two-week period of either real or sham 5-Hz rTMS. Participants were examined at baseline, after the first day of treatment, and after two weeks of rTMS treatment. Outcomes relevant to this review included ALSFRSr, FSS, and quality of life, measured using the MOS 36-Item Short Form Health Survey (SF-36).

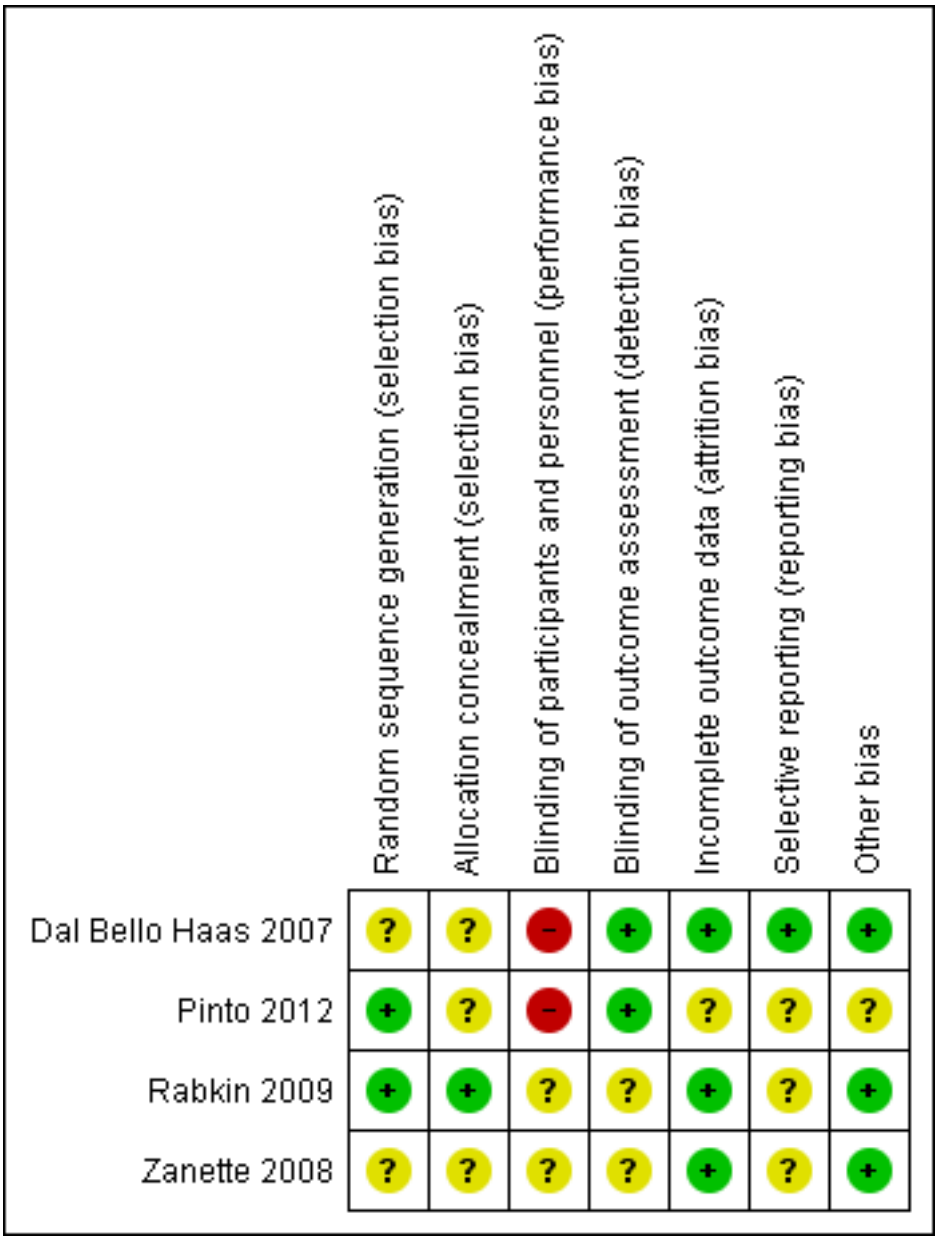
Excluded studies

We excluded 13 studies because (i) they were not RCTs (Carter 2005), (ii) did not assess fatigue as an end point (Drory 2001; Dupuis 2012; Goonetilleke 1995; Gordon 2007), or (iii) did not include a validated, patient-reported measure for fatigue (Bertorini 2011; Cudkowitz 2003; Desnuelle 2001; Lange 2006; Mazzini 2001; Rosenfeld 2009; Silva 2009; Steele 2004).

Risk of bias in included studies

Figure 2 shows the review authors' 'Risk of bias' assessments using the Cochrane 'Risk of bias' tool.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias domain for each included study.



The risk of bias in the included studies was generally unclear, as all study reports tended to omit important information concerning risk of bias. Eighteen of the 28 risk of bias domains were judged to be unclear. However, where this information was reported, the majority (7 out of 10) of the judgements were of a low risk of bias. Two cases in which risk of bias was judged to be high, related to blinding of participants and personnel. In one study the patients received training for the intervention and follow-up calls to ensure compliance from a physician who was aware of group allocation (Pinto 2012). In the other study, the participants and personnel were unblinded, however the outcome assessor was blinded and participants were asked not to reveal their assignment(Dal Bello Haas 2007). Although the dropout rate in this study was high, reasons for withdrawal were unrelated to the intervention and we considered the risk of attrition bias to be low. We assessed the risk of other bias as high for another study in which the dropout rate was high in the intervention arm (16%) (Rabkin 2009).

Effects of interventions

See: **Summary of findings for the main comparison** Modafinil compared to placebo in ALS/MND; **Summary of findings 2** Exercise compared to usual care in ALS/MND; **Summary of findings 3** Inspiratory muscle training compared to sham intervention in ALS/MND; **Summary of findings 4** Repetitive transcranial magnetic stimulation (rTMS) compared to sham intervention in ALS/MND

Modafinil versus placebo

Reported in Rabkin 2009. Of the 32 (25 intervention, 7 control) people randomised, 28 completed the four-week double-blind phase, with all four dropouts coming from the intervention group.

Primary outcome

Level of fatigue at the end of the follow-up period

The possible range in Fatigue Severity Scale (FSS, total) is from 9 to 63, with higher scores indicating more fatigue or more fatigue-related problems.

Level of fatigue was assessed using the FSS in an intention-to-treat (ITT) analysis. At the end of the follow-up period, the mean score in the modafinil group (adjusted mean (SE) 32 (3.6)) was lower than in the placebo group (adjusted mean (SE) 43 (5.0)) (MD -11.00, 95% CI -23.08 to 1.08; P = 0.066; Analysis 1.1).

We downgraded the quality of evidence to very low (-3): once for study limitations and twice for imprecision. The security of blinding in the trial was unclear and the report did not provide enough information to assess attrition and selective reporting. The trial was small and the 95% CI of the effect estimate included appreciable benefit and little or no effect. See Summary of findings for the main comparison.

Secondary outcomes

Sleepiness

The range of possible Epworth Sleepiness Scale (ESS) scores is from 0 to 24, with higher scores indicating more sleepiness.

Sleepiness was assessed using the ESS in an ITT analysis at the end of the follow-up period. There was little or no difference in adjusted mean scores (SE) for sleepiness between the modafinil group (5 (0.6)) and the placebo group (7 (1.1)) (MD -2.00, 95% CI -4.46 to 0.46; Analysis 1.1). The result was imprecise; 95% CI included both a potentially clinically relevant effect and no effect.

Depression

Scores in the Beck Depression Inventory-II (BDI-II) range from 0 to 63, with higher scores indicating greater severity of depressive symptoms.

The BDI-II was used to assess depression at the end of the follow-up period in an ITT analysis. There was no difference in adjusted mean score between the modafinil group (adjusted mean (SE) 9 (1.0)) and the placebo group (adjusted mean (SE) 9 (2.0)) (MD 0.00 95% CI -4.38 to 4.38; Analysis 1.1).

Quality of life

Not assessed.

Functional status

Not assessed using the ALS Functional Rating Scale (ALSFRS) or revised ALSFRS (ALSFRS-R).

Statistically significant improvements were demonstrated in the Clinical Global Impression Score (Chi^2 = 8.887, degrees of freedom (df) = 1; P = 0.003). Only 1/7 participants (14%) in the placebo group reported that they were much or very much improved, compared to 19/25 participants (75%) in the intervention group. All data were taken from the published report.

Adverse effects

Three participants in the modafinil group dropped out due to side effects (two with headache, one with tightness in chest); a fourth for lack of effect and burden of travel). A participant in the placebo group discontinued modafinil because of 'agitation' during a subsequent open-label phase of the study. Anxiety (in 2 participants), nausea (in 1), dizziness (in 1), and sialorrhoea (in 1, probably ALS-related) also occurred with treatment. Numerical analysis was not possible, as the number of participants with adverse events was not reported.

We downgraded the quality of evidence to very low (-3): once for study limitations and twice for imprecision. Reporting of adverse events was incomplete and security of blinding was unclear. The trial was small and the event rate low. See Summary of findings for the main comparison.

Resistance exercise versus usual care

Reported in Dal Bello Haas 2007. The study randomly assigned 27 people to receive resistance exercise (N = 13) or usual care (N = 14). Five participants from the intervention group and four participants from the control group dropped out for reasons unrelated to the tolerability of the intervention. Data represent an available case analysis of the remaining eight participants in the intervention group and 10 participants in the usual care group.

Primary outcome

Level of fatigue at the end of the follow-up period

Dal Bello Haas 2007 measured fatigue using the FSS at six months. The possible range in FSS (total) is from 9 to 63. Higher scores indicate more fatigue or more fatigue-related problems.

The intervention had little effect on fatigue, as scores on the FSS were 42.9 ± 8.7 in the intervention group (N = 8) and 42.7 ± 15.2 in the usual care group (N = 10) at six-month follow-up (MD 0.20, 95% CI -10.98 to 11.38; Analysis 2.3).

We downgraded the quality of evidence to very low (-3): once for study limitations (lack of blinding) and twice for imprecision, as the 95% CI included appreciable benefit and appreciable harm. See Summary of findings 2.

Secondary outcomes

Sleepiness

Not assessed.

Depression

Mental health was assessed using the Short Form-36 Health Survey (SF-36) Mental Health subscale, with a range of possible scores from 0 to 100, with a higher score indicating better health.

SF-36 Mental Health subscale scores (mean ± SD) showed no clear difference between the resistance exercise and usual care group at 6-month follow-up: 22.3 ± 4.0 in the resistance exercise group (N = 8) and 24.0 ± 4.2 in the usual care group (N = 10) (MD -1.70, 95% CI -5.50 to 2.10; Analysis 2.3).

Quality of life

Quality of life was assessed using the eight subscales of the SF-36, including mental health, reported above. All of the SF-36 scales have scores that range from 0 to 100, with higher scores indicating a more favourable state.

The study reported less impairment in physical function in the resistance exercise group (N = 10) than in the usual care group (N = 8) at six-months follow-up: intervention group (mean ± SD) 21.1 ± 7.6 versus usual care group 14.0 ± 3.9 (MD 7.10, 95% CI 1.31 to 12.89; Analysis 2.3).

The trial found little or no differences between the resistance exercise (N = 10) and usual care group (N = 8) on any other SF-36 subscale (Analysis 2.3): Physical Role subscale (mean ± SD): resistance exercise group 5.1 ± 1.0, usual care 4.9 ± 1.7 (MD 0.20, 95% CI -1.06 to 1.46}; Pain subscale: resistance exercise 10.2 ± 2.3, usual care 10.3 ± 1.7 (MD -0.10, 95% CI -2.01 to 1.81); General Health subscale: resistance exercise 16.4 ± 3.4, usual care 16.0 ± 6.6 (MD 0.40, 95% CI -4.32 to 5.12); Vitality subscale: resistance exercise 16.4 ± 3.4, usual care 14.8 ± 4.1 (MD 1.60, 95% CI -1.87 to 5.07); Social Function subscale: resistance exercise 8.4 ± 1.5, usual care 7.7 ± 2.1 (MD 0.7, 95% CI -0.97 to 2.37); and Emotional Role subscale: resistance exercise group 5.3 ± 0.9, usual care 4.7 ± 1.4 (MD 0.60, 95% CI -0.47 to 1.67).

Functional status

The study demonstrated less decline in physical function overall in the resistance exercise group: resistance exercise group (mean ± SD) 33.8 ± 4.7, usual care 28.1 ± 4.8 (MD 5.7, 95% CI 1.29 to 10.11) and in the lower extremities: intervention group 18.8 ± 4, usual care 13.5 ± 3.4 (MD 5.50, 95% CI 1.82 to 8.78) (Analysis 2.3).

Adverse effects

None of the participants who discontinued did so because they thought the exercise programme itself was making their condition worse. No participants reported excessive soreness, cramping, or fatigue with either exercise protocol.

We downgraded the quality of evidence to very low (-3): once for study limitations (lack of blinding) and twice for imprecision, as the 95% CI included appreciable benefit and appreciable harm. See Summary of findings 2.

Respiratory exercise versus sham intervention

Pinto 2012 randomised 26 participants to receive resistance exercise (N = 13) or sham intervention (N = 13), of whom 12 in each group were evaluable. Due to the delayed-start design for the control group, we only considered the results of the first four months of the intervention, during which we could compare the active and sham groups.

Primary outcome

Level of fatigue at the end of the follow-up period

Fatigue was assessed using the FSS, with a possible total range from 9 to 63. Higher scores indicate more fatigue or more fatigue-related problems.

At the end of the first follow-up period the intervention group showed less fatigue than the sham intervention group (MD -9.65, 95% CI -22.04 to 2.73; N = 24; Analysis 3.1).

We downgraded the quality of evidence to very low (-3): twice for imprecision and once for study limitations. The trial was very small and 95% CI included appreciable benefit and little or no effect. The nature of the intervention meant that the trainer was aware of the intervention group. See Summary of findings 3.

Secondary outcomes

Sleepiness

The range of possible ESS scores is from 0 to 24. Higher scores indicate more sleepiness.

We found no clear differences between groups in mean scores on the ESS questionnaire at the end of the first follow-up period (MD 0.31, 95% CI -3.48 to 4.10; N = 24; Analysis 3.1).

Depression

The range of possible Hamilton Depression Rating Scale (HDRS, or Ham-D) scores, which was used to measure depression, is from 0 to 63. Higher scores indicate greater severity of depression.

Depression was lower in the respiratory exercise group than the usual care group at the end of the first follow-up period (MD 1.77, 95% CI 0.02 to 3.52; N = 24; Analysis 3.1).

Quality of life

Quality of life was assessed using the EuroQol - 5 dimension instrument (EQ-5D), with a range in scores from 1 to 25. Higher scores indicate lower health-related quality of life.

There was no significant difference in quality of life at the end of the first follow-up period between the resistance exercise and the usual care groups (MD 0.77, 95% CI -17.10 to 18.63; N = 24; Analysis 3.1).

Functional status

Functional status was assessed with the ALSFRS, administered by a blinded evaluator. There was no difference between groups in mean scores for the overall scale at the end of the first follow-up (MD 0.85, 95% CI -2.16 to 3.85; N = 24), the ALSFRS-b bulbar subscale (MD -0.39, 95% CI -1.38 to 0.61; N = 24), or the respiratory subscale (MD 0.08, 95% CI -0.25 to 0.41; N = 24; Analysis 3.1).

Adverse effects

There were no adverse effects reported.

We downgraded the quality of evidence for this outcome to very low (-3): twice for imprecision and once for study limitations. The trial was very small. The nature of the intervention meant that the trainer was aware of the intervention group. See Summary of findings 3.

Repetitive transcranial magnetic stimulation (rTMS) versus sham intervention

Zanette 2008 randomised 10 participants to receive rTMS (N = 5) or the sham intervention (N = 5).

Primary outcome

Level of fatigue at the end of the follow-up period

Fatigue was measured using the FSS, and assessed using two-way repeated measures analysis of variance (ANOVA; the within-subjects factor was time and the between-subjects factor was treatment arm). The paper reported a significant effect from rTMS for fatigue at the end of the two-week follow-up period ($F_{[2,16]} = 4.0$; P = 0.04; Analysis 4.1). The effect was non-significant following post hoc Bonferroni adjustments (data not reported). The paper did not provide mean scores, SDs, or CIs.

We downgraded the quality of evidence to very low (-3): once for study limitations and twice for imprecision. The trial involved 10 people. The risk of bias was unclear, as the trial report provided too little detail for assessment. See Summary of findings 4.

Secondary outcomes

Sleepiness

Not assessed.

Depression

Not assessed.

Quality of life

Quality of life was assessed using the global score from the SF-36, a method for which there is no evidence of psychometric validity (Ware 1992).

Functional status

The ALSFRSr was used to assess functional status at the end of the follow-up period, using complete data. ANOVA tests demonstrated no significant interaction between time and treatment ($F_{[2,16]} = 2.7$; $P > 0.05$; Analysis 4.1). The paper did not report mean scores, SDs, or CIs.

Adverse effects

No adverse events were reported.

DISCUSSION

Summary of main results

We included four studies (86 participants) that met the eligibility criteria in this review. They evaluated pharmacological interventions (modafinil) (Rabkin 2009) and non-pharmacological interventions, including resistance exercise (Dal Bello Haas 2007), respiratory exercise (Pinto 2012), and repetitive transcranial magnetic stimulation (rTMS) (Zanette 2008) We are very uncertain about the effects of these interventions on fatigue in ALS, as the quality of evidence was too low to rule out any negative effect or establish clinical benefit.

Rabkin 2009 (32 participants) conducted an ITT analysis that showed improved fatigue at the end of a brief double-blind phase for the modafinil group, although the 95% CI were wide, and allowed for the possibility of no effect.

Resistance exercise had little effect on fatigue in Dal Bello Haas 2007 (27 participants).

In Pinto 2012 (26 participants), there was reduced fatigue in the respiratory exercise group over the sham intervention group, but the results were imprecise and 95% CI were consistent with both a large effect and none. No clear differences between groups were reported for sleepiness, quality of life, or functional status, but there was small reduction of depressive symptoms in the respiratory exercise group.

Zanette 2008 (10 participants) reported that improvements in fatigue in the rTMS group showed a "trend towards" statistical significance before post hoc tests corrected for multiple comparisons. These effects were short-lived, and after two weeks with no treatment, the trialists reported that there was no clear difference between the two groups on any of the reported outcomes.

In the modafinil study, three participants dropped out from the intervention arm due to side effects including headache and headache with chest tightness. The trial authors noted that similar adverse events were not reported in another RCT they had run with over 100 people with HIV/AIDS (Rabkin 2009). Similarly, an open-label trial of modafinil for ALS/MND reported that the drug was well tolerated in both the 200 mg and 400 mg groups (Carter 2005). Rabkin and colleagues also ran a completer's analysis, in which the positive effect of modafinil in alleviating fatigue was more pronounced, with effect sizes significant at the 5% level for fatigue, sleepiness, energy, and stamina (Rabkin 2009).

No adverse events were reported in any of the non-pharmacological trials.

Overall completeness and applicability of evidence

We identified four studies. Each evaluated different interventions which, at best, reported weak or transient beneficial effects. The heterogeneity in the assessed interventions precluded meta-analysis of the disparate outcomes. Therefore, no reliable information was available to assess whether different treatments for fatigue may be beneficial or harmful for people with ALS/MND.

This review highlights a clear need to commit high-quality evidence to the corpus of literature relating to treatment for fatigue in people with ALS/MND.

Quality of the evidence

We assessed the overall risk of bias from low to unclear for two of the four studies. We found issues relating to blinding of participants or personnel in two of the trials. In Pinto 2012, the trainer was aware of the group allocation and in Dal Bello Haas 2007, the participants were unblinded due to the nature of the intervention. Though they were asked not to reveal their allocation to the assessors, no formal evaluation took place to confirm that assessors remained unblinded throughout the trial period. High dropout introduced a high risk of bias for the study by Rabkin and colleagues of modafinil versus placebo (Rabkin 2009). It is notable that more than half of the risk of bias domains could not be ascertained from the published reports. All results lacked precision and were based on findings from single small studies. There is an additional risk that we were unable to identify all relevant controlled research studies, due to publication bias.

Potential biases in the review process

We followed the Cochrane Neuromuscular search strategies, which include a search of the Cochrane Neuromuscular Specialised Register, which is updated weekly to monthly from a range of databases. Therefore, it is unlikely that studies have been missed, although it is possible that studies that have not been published could be missing. Should any further studies be identified, we will include them in future updates of the review. We followed the recommended Cochrane review process to reduce potential biases, which included having at least two review authors independently assess identified studies, extract data, and evaluate risk of bias. The small size of included studies means that estimates of adverse event rate frequency are unlikely to be accurate, particularly for rare events.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other systematic reviews on this topic for people with ALS/MND.

AUTHORS' CONCLUSIONS

Implications for practice

There is very limited and low-quality evidence from randomised controlled trials (RCTs) about treatment to reduce fatigue in amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). Therefore, it is uncertain whether modafinil, breathing exercises, resistance exercise, or repetitive transcranial magnetic stimulation (rTMS) are of benefit.

Implications for research

Despite the prevalence of fatigue in ALS/MND, we lack high-quality RCTs that evaluate interventions to improve this disabling, but potentially treatable symptom. There is a need for considerable further work to identify an effective treatment for fatigue for people with ALS/MND. Three studies demonstrated very low quality evidence of benefit for modafinil, inspiratory muscle training, and rTMS, which may merit further investigation. Unfortunately, the positive effects of rTMS were short lived, and no longer detected two weeks after treatment cessation. Although the effect of modafinil and respiratory exercise is very uncertain, as the quality of the evidence is very low, they appear to have the greatest potential as an effective treatment for fatigue in ALS/MND.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dal Bello Haas 2007

Methods	Randomised, placebo-controlled trial
Participants	27 people with a diagnosis of clinically definite, probable, or laboratory-supported ALS, FVC of 90% or greater, and an ALSFRS score of 30 or greater. Mean age in years (SD): resistance exercise 56 (7); control 51 (7)

Dal Bello Haas 2007 *(Continued)*

	Gender (% female): resistance exercise 4 (30.8%); control 7 (50%) Mean time since diagnosis in months (SD): resistance exercise 20 (12); control 15 (13)
Interventions	**Intervention** (N = 13) Moderate-load and moderate-intensity resistance exercise programme and stretching for upper and lower extremities. Intervention participants received a personalised 'moderate intensity resistance exercise programme' by an unblinded research physical therapist. The programmes were developed according to individual tolerance and limitations. **Control** (N = 14) Stretching exercises for upper and lower extremities only.
Outcomes	**Primary** Change in global function measured on the ALSFRS at 6 months **Secondary** Fatigue, measured on the FSS Quality of life, measured on SF-36
Funding	Funded by the ALS Association (US)
Conflicts of interest	The authors report no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed. Described as "randomized" but details of randomisation process not described.
Allocation concealment (selection bias)	Unclear risk	Participants assigned by "selecting an opaque envelope that contained group assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded. In addition, the trial authors reported that "[t]he physical therapists who initially prescribed the exercise programs were unblinded to group assignment and were responsible for collecting the logs, making the telephone contacts, interviewing subjects about exercise side effects and compliance, and revising the exercise program."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessor blinded. Participants asked not to reveal allocation to assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 usual care participants (40%) and five resistance participants (62.5%) did not complete the study (P = 0.70). Two participants from each arm who dropped out were taking riluzole. No participants who discontinued did so because they believed that the exercise programme itself was worsening their condition.
Selective reporting (reporting bias)	Low risk	All outcomes reported in ClinicialTrials.gov registration
Other bias	Low risk	No other biases apparent

Pinto 2012

Methods	RCT with delayed-start design
Participants	26 people with ALS/MND with normal respiratory function. Mean age in years (SD): intervention 57 (9); control 56 (8) Gender (% female): intervention 6 (46.1%); control 2 (15.4%) Mean time since diagnosis in months (SD): intervention 11 (5); control 12 (6)
Interventions	Respiratory exercise using a inspiratory muscular training (IMT) device. All participants instructed to use the IMT twice daily; each session 10 minutes **Intervention** (N = 13) In the intervention groups the resistance was set to between 30% to 40% of maximum inspiratory pressure (MIP). Participants started the exercise programme at entry and were followed for 8 months. **Control** (N = 13) Sham exercise programme. In the sham intervention group the resistance in the IMT was set to the lowest possible level. Participants followed a placebo exercise programme at entry, then the active exercise programme for 4 months.
Outcomes	**Primary** Functional status, measured by the ALSFRS **Secondary** Respiratory tests Neurophysiological measurements Fatigue, measured on the FSS Depression, measured on the Hamilton Rating Scale for Depression Sleepiness, measured on the ESS Functional Independence, measured on Functional Independence Measure Quality of life, measured on EuroQoL-5D
Funding	Fundacão para a Ciência e a Tecnologia
Conflicts of interest	The authors report no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants independently randomised in blocks of 6
Allocation concealment (selection bias)	Unclear risk	Not discussed

Pinto 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Trainer aware of participants group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ALSFRS administered by a blind assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	For one analysis, incomplete data imputed as 25% of the lower percentile value observed in the remaining participants of the same group
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Not discussed

Rabkin 2009

Methods	RCT with 3:1 (intervention:placebo) randomisation
Participants	32 participants with probable or definite ALS by modified El Escorial criteria, FVC ≥ 50% and able to communicate verbally or with an assistive device. Mean age in years (SD): modafinil 59 (13); placebo 56 (5) Gender (% female): modafinil 11 (44%); placebo 3 (43%) Mean time since diagnosis in months (SD): modafinil 16 (18); placebo 29 (33)
Interventions	**Intervention** (N = 25) Modafinil in doses beginning with 100 mg/day and increasing in the event of no response to 300 mg/day for four weeks **Control** (N = 7) Placebo
Outcomes	**Primary** Clinical Global Impressions scale **Secondary** FSS ESS
Funding	Not reported
Conflicts of interest	The authors report no conflicts of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Rabkin 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	"3:1 block randomisation provided by the Research Pharmacy at New York State Psychiatric Institute"
Allocation concealment (selection bias)	Low risk	"The sequence was concealed until the intervention was assigned"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was maintained and assessed for both doctor and participants, but "blinding was questionable since participants knew there was a 3:1 chance of getting modafinil versus placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	16% dropout, 9% due to adverse events. However, there were complete data for the outcomes of interest in this review.
Selective reporting (reporting bias)	Unclear risk	No protocol or prespecified outcomes
Other bias	Low risk	No other biases apparent

Zanette 2008

Methods	Pilot RCT
Participants	10 people with probable or definite ALS/MND randomised. Mean age in years (SD): intervention 59(9); control 60(9) Gender (% female): intervention 1 (20%); control 3 (60%) Mean time since diagnosis in months (SD): intervention 11 (3); control 12 (4).
Interventions	**Intervention** (N = 5) Daily repetitive transcranial magnetic stimulation (5Hz) on upper- and lower-limb cortical areas **Control** (N = 5) Sham stimulation using a specific sham coil that provided no cortical stimulation but did produce similar auditory and scalp sensations 2 weeks' treatment
Outcomes	Functional status, measured on the ALSFRS-R Fatigue, measured on the FSS Medical Research Council (MRC) strength score Maximum voluntary isometric contraction (MVIC) for upper and lower limbs Outcomes measured 2 weeks after the end of treatment
Funding	Not reported
Conflicts of interest	Not reported

Zanette 2008 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"[Participants] were allocated to the treatment: 5 active and 5 sham stimulation"
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Use of sham treatment suggests that participants were blinded; but no explicit mention of blinding made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four week assessments available for all randomised participants
Selective reporting (reporting bias)	Unclear risk	No protocol or prespecified outcomes
Other bias	Low risk	No other biases apparent

ALS: amyotrophic lateral sclerosis; ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; ESS: Epworth Sleepiness Scale; FSS: Fatigue Severity Scale; FVC: forced vital capacity; SD: standard deviation; SF-36: Short Form 36 Health Survey

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bertorini 2011	No validated, patient-reported fatigue outcome (study used VAS for fatigue). Double-blind crossover trial to assess tolerability of 3-4 diaminopyridine (3,4-DAP)
Carter 2005	Non-randomised study. Open-label trial of modafinil. 2-week trial of 200 mg or 400 mg doses. Significant reductions in fatigue (FSS) and sleepiness (ESS) evident after 2 weeks
Cudkowitz 2003	No validated, patient-reported fatigue outcome (study used maximum voluntary isometric contraction). RCT of topiramate to slow disease progression
Desnuelle 2001	No validated, patient-reported fatigue outcome (study used VAS for fatigue). Double-blind trial to assess efficacy of alpha-tocopherol (vitamin E) to treat ALS/MND
Drory 2001	Fatigue not assessed as primary or secondary end point
Dupuis 2012	Fatigue not assessed as primary or secondary end point
Goonetilleke 1995	Fatigue not assessed as primary or secondary end point

Study	Reason for exclusion
Gordon 2007	Fatigue not assessed as primary or secondary end point
Lange 2006	Fatigue assessed using individual items from a validated scale, not the validated scale itself
Mazzini 2001	Fatigue not assessed using validated, patient-reported outcome measure
Rosenfeld 2009	Fatigue not assessed using validated, patient-reported outcome measure
Silva 2009	Fatigue not assessed using validated, patient-reported outcome measure
Steele 2004	Fatigue not assessed using validated, patient-reported outcome measure

ALS/MND: amyotrophic lateral sclerosis/motor neuron disease; ESS: Epworth Sleepiness Scale; FSS: fatigue severity scale; VAS: visual analogue scale

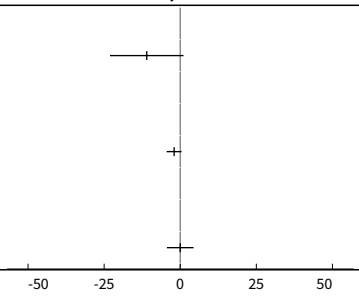
DATA AND ANALYSES

Comparison 1. Modafinil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Efficacy outcomes (all at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Fatigue (FSS)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sleepiness	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Depression	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Modafinil versus placebo, Outcome 1 Efficacy outcomes (all at 4 weeks).

Study or subgroup	Modafinil N	Modafinil Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.1.1 Fatigue (FSS)						
Rabkin 2009	25	32 (18)	7	43 (13.2)		-11[-23.08,1.08]
1.1.2 Sleepiness						
Rabkin 2009	25	5 (3)	7	7 (2.9)		-2[-4.46,0.46]
1.1.3 Depression						
Rabkin 2009	25	9 (5)	7	9 (5.3)		0[-4.38,4.38]



Comparison 2. Resistance exercise versus usual care

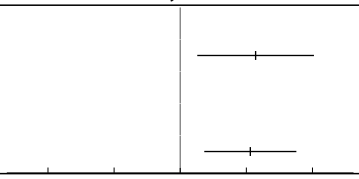
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue (at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Fatigue (FSS)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Functional status (at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Functional status (ALSFRS total score)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Functional status (ALFRS lower extremity)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Quality of life (at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mental health (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Physical function (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Physical role (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Pain (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 General health (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Vitality (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Social function (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 Emotional role (SF-36)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Resistance exercise versus usual care, Outcome 1 Fatigue (at 6 months).

Study or subgroup	Exercise N	Exercise Mean(SD)	Usual care N	Usual care Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.1.1 Fatigue (FSS)						
Dal Bello Haas 2007	8	42.9 (8.7)	10	42.7 (15.2)		0.2[-10.98,11.38]

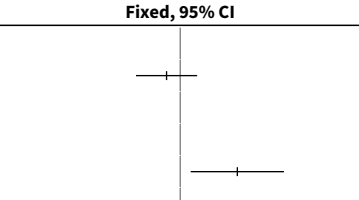
Analysis 2.2. Comparison 2 Resistance exercise versus usual care, Outcome 2 Functional status (at 6 months).

Study or subgroup	Exercise N	Exercise Mean(SD)	Usual care N	Usual care Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.2.1 Functional status (ALSFRS total score)						
Dal Bello Haas 2007	8	33.8 (4.7)	10	28.1 (4.8)		5.7[1.29,10.11]
2.2.2 Functional status (ALFRS lower extremity)						
Dal Bello Haas 2007	8	18.8 (4)	10	13.5 (3.4)		5.3[1.82,8.78]



Analysis 2.3. Comparison 2 Resistance exercise versus usual care, Outcome 3 Quality of life (at 6 months).

Study or subgroup	Exercise N	Exercise Mean(SD)	Usual care N	Usual care Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.3.1 Mental health (SF-36)						
Dal Bello Haas 2007	8	22.3 (4)	10	24 (4.2)		-1.7[-5.5,2.1]
2.3.2 Physical function (SF-36)						
Dal Bello Haas 2007	8	21.1 (7.6)	10	14 (3.9)		7.1[1.31,12.89]
2.3.3 Physical role (SF-36)						
Dal Bello Haas 2007	8	5.1 (1)	10	4.9 (1.7)		0.2[-1.06,1.46]
2.3.4 Pain (SF-36)						
Dal Bello Haas 2007	8	10.2 (2.3)	10	10.3 (1.7)		-0.1[-2.01,1.81]
2.3.5 General health (SF-36)						
Dal Bello Haas 2007	8	16.4 (3.4)	10	16 (6.6)		0.4[-4.32,5.12]
2.3.6 Vitality (SF-36)						
Dal Bello Haas 2007	8	16.4 (3.4)	10	14.8 (4.1)		1.6[-1.87,5.07]
2.3.7 Social function (SF-36)						
Dal Bello Haas 2007	8	8.4 (1.5)	10	7.7 (2.1)		0.7[-0.97,2.37]
2.3.8 Emotional role (SF-36)						
Dal Bello Haas 2007	8	5.3 (0.9)	10	4.7 (1.4)		0.6[-0.47,1.67]



Comparison 3. Respiratory exercise versus sham intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Efficacy outcomes (all at 4 months)			Other data	No numeric data
1.1 Fatigue (FSS)			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 Sleepiness			Other data	No numeric data
1.3 Depression			Other data	No numeric data
1.4 Quality of life			Other data	No numeric data
1.5 Functional status			Other data	No numeric data
1.6 Functional status (ALSFRS-bulbar)			Other data	No numeric data
1.7 Functional status (ALSFRS-respirato-ry)			Other data	No numeric data

Analysis 3.1. Comparison 3 Respiratory exercise versus sham intervention, Outcome 1 Efficacy outcomes (all at 4 months).

	Efficacy outcomes (all at 4 months)		
Study	Respiratory exercise N	Sham intervention N	MD, 95% CI
Fatigue (FSS)			
Pinto 2012	12	12	-9.654, 95% CI -22.037 to 2.729
Sleepiness			
Pinto 2012	12	12	0.308, 95% CI -3.48 to 4.096
Depression			
Pinto 2012	12	12	1.769, 95% CI 0.018 to 3.52
Quality of life			
Pinto 2012	12	12	0.769, 95% CI -17.093 to 18.631
Functional status			
Pinto 2012	12	12	0.846, 95% CI -2.157 to 3.849
Functional status (ALSFRS-bulbar)			
Pinto 2012	12	12	-0.385, 95% CI -1.378, to 0.609
Functional status (ALSFRS-respiratory)			
Pinto 2012	12	12	0.077, 95% CI -0.254 to 0.407

Comparison 4. Repetitive transcranial magnetic stimulation (rTMS) versus sham intervention

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Efficacy outcomes (all at 2 weeks)			Other data	No numeric data
1.1 Fatigue (FSS)			Other data	No numeric data
1.2 Functional status			Other data	No numeric data

Analysis 4.1. Comparison 4 Repetitive transcranial magnetic stimulation (rTMS) versus sham intervention, Outcome 1 Efficacy outcomes (all at 2 weeks).

	Efficacy outcomes (all at 2 weeks)	
Study	Number of participants	Analysis of variance (time x treatment arm
	Fatigue (FSS)	
Zanette 2008	10 (5 rTMS, 5 sham intervention)	$F_{[2,16]} = 4.0$; P = 0.04
	Functional status	
Zanette 2008	10 (5 rTMS, 5 sham intervention)	$F_{[2,16]} = 2.7$; P > 0.05

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL via CRS-W) search strategy

#1 MeSH DESCRIPTOR Motor Neuron Disease Explode All AND CENTRAL:TARGET
#2 "motor neuron disease*" or "motor neurone disease*" AND CENTRAL:TARGET
#3 "motoneuron disease*" or "motoneurone disease*" AND CENTRAL:TARGET
#4 "motorneuron disease*" or "motorneurone disease*" AND CENTRAL:TARGET
#5 "charcot disease" AND CENTRAL:TARGET
#6 "amyotrophic lateral sclerosis" AND CENTRAL:TARGET
#7 als:ti or als:ab or nmd:ti or mnd:ab AND CENTRAL:TARGET
#8 #1 or #2 or #5 or #6 or #7 AND CENTRAL:TARGET
#9 fatigue or tired* or weariness or weary or exhaust* or lacklustre AND CENTRAL:TARGET
#10 astheni* or lethargic or languidness or languor or lassitude or listlessness AND CENTRAL:TARGET
#11 (lack or loss or lost) near2 (energy or vigour or vigour) AND CENTRAL:TARGET
#12 #9 or #10 or #11 AND CENTRAL:TARGET
#13 #8 and #12 AND CENTRAL:TARGET
#14 MeSH DESCRIPTOR Exercise Therapy Explode All AND CENTRAL:TARGET
#15 MeSH DESCRIPTOR Physical Therapy Modalities Explode All AND CENTRAL:TARGET
#16 rehabilitation or exercise or train or activity or physical or strength or sports AND CENTRAL:TARGET
#17 isometric or isotonic or isokinetic or endurance or kinesiotherap* AND CENTRAL:TARGET
#18 "relaxation therapy" or "behavior therapy" or "behaviour therapy" or "orthotic devices" AND CENTRAL:TARGET
#19 exercise near2 (grading or pacing) AND CENTRAL:TARGET
#20 MeSH DESCRIPTOR Drug Therapy Explode All AND CENTRAL:TARGET
#21 "cognitive therapy" AND CENTRAL:TARGET
#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 AND CENTRAL:TARGET
#23 #13 and #22 AND CENTRAL:TARGET
#24 #13 and #22 AND CENTRAL:TARGET
#25 (#13 and #22) AND (INREGISTER)
#26 181:zsen AND INREGISTER AND ISINCENTRAL
#27 181:zsen AND INSEGMENT AND ISINCENTRAL
#28 #26 OR #27
#29 #24 not #28
#3 "motoneuron disease*" or "motoneurone disease*" AND CENTRAL:TARGET
#30 #25 not #26
#31 #29 OR #30

Appendix 2. MEDLINE Ovid SP search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Ovid MEDLINE(R) 1946 to August Week 4 2017

Search Strategy:
---
1 randomized controlled trial.pt. (476988)
2 controlled clinical trial.pt. (96146)
3 randomized.ab. (417587)

4 placebo.ab. (194961)
5 drug therapy.fs. (2045786)
6 randomly.ab. (289174)
7 trial.ab. (438850)
8 groups.ab. (1782381)
9 or/1-8 (4222639)
10 exp animals/ not humans.sh. (4531946)
11 9 not 10 (3650505)
12 exp Motor Neuron Disease/ (24501)
13 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease$1).mp. (8212)
14 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (179)
15 charcot disease.tw. (21)
16 amyotrophic lateral sclerosis.tw. (19305)
17 or/12-16 (32403)
18 Fatigue/ or fatigue.mp. (92934)
19 (tired$ or weariness or weary or exhaust$ or lacklustre or astheni$ or lethargic or languidness or languor or lassitude or listlessness).mp. (60396)
20 ((lack or loss or lost) adj2 (energy or vigour or vigour)).mp. (6665)
21 18 or 19 or 20 (154071)
22 17 and 21 (335)
23 Fatigue/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (2687)
24 exp Exercise Therapy/ (42299)
25 exp Physical Therapy Modalities/ (135665)
26 rehabilitation.mp. or Rehabilitation/ (161213)
27 (exercise or train or activity or physical or exercise or strength or sports or isometric or isotonic or isokinetic or endurance or kinesiotherap$).mp. (3621760)
28 relaxation therapy/ (6260)
29 (exercise adj2 (grading or pacing)).mp. (191)
30 behavior therapy/ (26836)
31 orthotic devices/ (6354)
32 exp drug therapy/ (1261528)
33 cognitive therapy/ (21880)
34 or/23-33 (4918512)
35 11 and 22 and 34 (63)
36 exp *neoplasms/ (2682771)
37 35 not 36 (62)
38 remove duplicates from 37 (56)

Appendix 3. Embase Ovid SP search strategy

Database: Embase <1980 to 2017 Week 36>
Search Strategy:
---
1 crossover-procedure.sh. (53004)
2 double-blind procedure.sh. (139660)
3 single-blind procedure.sh. (29379)
4 randomized controlled trial.sh. (467233)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1418321)
6 trial.ti. (228280)
7 or/1-6 (1579561)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1664741)
9 animal/ or nonanimal/ or animal experiment/ (3783510)
10 9 not 8 (3138210)
11 7 not 10 (1452500)
12 limit 11 to (conference abstracts or embase) (1224945)
13 Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ (36673)
14 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (11958)
15 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (195)
16 charcot disease.tw. (26)
17 amyotrophic lateral sclerosis.tw. (24487)
18 or/13-17 (40610)
19 Fatigue/ or fatigue.mp. (208432)

20 (tired$ or weariness or weary or exhaust$ or lacklustre or astheni$ or lethargic or languidness or languor or lassitude or listlessness).mp. (103622)
21 ((lack or loss or lost) adj2 (energy or vigour or vigour)).mp. (6165)
22 19 or 20 or 21 (301269)
23 18 and 22 (881)
24 fatigue/dm, dt, th [Disease Management, Drug Therapy, Therapy] (3699)
25 exp Exercise Therapy/ (63627)
26 exp Physical Therapy Modalities/ (75181)
27 rehabilitation.mp. or Rehabilitation/ (307922)
28 (exercise or train or activity or physical or exercise or strength or sports or isometric or isotonic or isokinetic or endurance or kinesiotherap$).mp. (4764154)
29 relaxation therapy/ (9816)
30 (exercise adj2 (grading or pacing)).mp. (217)
31 behavior therapy/ (40378)
32 orthotic devices/ (5247)
33 exp drug therapy/ (2093882)
34 cognitive therapy/ (42135)
35 or/24-34 (6755799)
36 11 and 23 and 35 (91)
37 exp *neoplasm/ (2854492)
38 36 not 37 (85)
39 remove duplicates from 38 (80)

Appendix 4. PsycINFO Ovid SP search strategy

Database: PsycINFO <1806 to August Week 4 2017>
Search Strategy:
---
1 (random$ or rct or cct or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (308023)
2 amyotrophic lateral sclerosis/ (3288)
3 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease$1).mp. (1243)
4 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (49)
5 or/2-4 (4107)
6 (fatigue or tired$ or weariness or weary or exhaust$ or lacklustre or astheni$ or lethargic or languidness or languor or lassitude or listlessness).mp. (38405)
7 ((lack or loss or lost) adj2 (energy or vigour or vigour)).mp. (619)
8 6 or 7 (38838)
9 1 and 5 and 8 (3)

Appendix 5. CINAHL Plus EBSCO host search strategy

Tuesday, September 05, 2017 9:18:08 AM
S30 S28 AND S29 2
S29 EM 20161007- 248,271
S28 S27 Limiters - Exclude MEDLINE records
Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 20
S27 S18 AND S23 AND S26 98
S26 S24 OR S25 40,470
S25 (lack or loss or lost) N2 (energy or vigour or vigour) 665
S24 fatigue or tired* or weariness or weary or exhaust* or lacklustre or astheni* or lethargic or languidness or languor or lassitude or listlessness 39,965
S23 S19 or S20 or S21 or S22 7,560
S22 (Lou Gehrig* W5 syndrome*) or (Lou Gehrig* w5 disease*) 42
S21 "amyotrophic lateral sclerosis" 3,397
S20 motor neuron disease or motor neurone disease or motoneuron* disease or motorneuron* disease 1,431
S19 (MH "Motor Neuron Diseases+") 6,785
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 990,862
S17 ABAB design* 102
S16 TI random* or AB random* 223,975

S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 447,954
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 171,024
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 59,093
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 34,513
S11 PT ("clinical trial" or "systematic review") 132,151
S10 (MH "Factorial Design") 1,005
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 315,906
S8 (MH "Meta Analysis") 28,517
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 92
S6 (MH "Quasi-Experimental Studies") 8,580
S5 (MH "Placebos") 10,318
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 36,327
S3 (MH "Clinical Trials+") 220,329
S2 (MH "Crossover Design") 15,021
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 77,258

Appendix 6. ERIC EBSCO host search strategy

Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - ERIC

Tuesday, September 05, 2017 9:40:20 AM

S8 S4 AND S7 1
S7 S5 OR S6 3,217
S6 (lack or loss or lost) N2 (energy or vigour or vigour) 97
S5 fatigue or tired* or weariness or weary or exhaust* or lacklustre or astheni* or lethargic or languidness or languor or lassitude or listlessness 3,125
S4 S1 OR S2 OR S3 47
S3 (Lou Gehrig* W5 syndrome*) or (Lou Gehrig* w5 disease*) 6
S2 amyotrophic lateral sclerosis 33
S1 motor neuron disease or motor neurone disease or motoneuron* disease or motorneuron* disease

CONTRIBUTIONS OF AUTHORS

Professor Carolyn Young conceived of the review.

All authors assisted in designing the review and the search strategies detailed in this review.

All authors assisted in drafting and providing critical appraisal of this review.

DECLARATIONS OF INTEREST

CG: no conflicts of interest.

FP: no conflicts of interest.

TF has received personal fees for consultancies (including data monitoring committees) from AstraZeneca, Bayer, Boehringer Ingelheim, CTCT, DaiichiSankyo, Feldmann Patent Attourneys, Galapagos, Grünenthal, Janssen, Mediconomics, Novartis, Parexel, Penumbra, Pharmalog, Roche, SGS, and UCB, but not for the indication concerned (fatigue in ALS/MND).

CY has published on fatigue in various neurological conditions, including MND, and advised a pharmaceutical company about a potential trial for fatigue in multiple sclerosis.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included an explanation of the process of downgrading the evidence in 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [*complications]; Benzhydryl Compounds [*therapeutic use]; Breathing Exercises [*methods]; Fatigue [etiology] [*therapy]; Modafinil; Randomized Controlled Trials as Topic; Resistance Training [*methods]; Transcranial Magnetic Stimulation [*methods]

MeSH check words

Humans