Interventions for post-stroke fatigue (Review)

McGeough E, Pollock A, Smith LN, Dennis M, Sharpe M, Lewis S, Mead GE

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Interventions for post-stroke fatigue

Elizabeth McGeough[2], Alex Pollock[3], Lorraine N Smith[4], Martin Dennis[5], Michael Sharpe[6], Susan Lewis[1], Gillian E Mead[1]

[1]School of Clinical Sciences and Community Health, University of Edinburgh, Edinburgh, UK. [2]Care of the Elderly Department, Edinburgh Royal Infirmary, Edinburgh, UK. [3]Nursing, Midwifery and Allied Health Professions Research Unit, Glasgow Caledonian University, Glasgow, UK. [4]Nursing and Health Care, Faculty of Medicine, University of Glasgow, Glasgow, UK. [5]Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK. [6]School of Molecular & Clinical Medicine, University of Edinburgh, Edinburgh, UK

Contact address: Gillian E Mead, School of Clinical Sciences and Community Health, University of Edinburgh, Room F1424, Royal Infirmary, Little France Crescent, Edinburgh, EH16 4SA, UK. gillian.e.mead@ed.ac.uk. gmead@staffmail.ed.ac.uk.

Editorial group: Cochrane Stroke Group.
Publication status and date: New, published in Issue 3, 2009.
Review content assessed as up-to-date: 6 October 2008.

Citation: McGeough E, Pollock A, Smith LN, Dennis M, Sharpe M, Lewis S, Mead GE. Interventions for post-stroke fatigue. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD007030. DOI: 10.1002/14651858.CD007030.pub2.

ABSTRACT

Background

Fatigue after stroke is common and distressing to patients. The best way to treat this fatigue is uncertain. Theoretically, several different interventions may be of benefit.

Objectives

To determine whether any treatment for fatigue after stroke reduces the proportion of patients with fatigue, or fatigue severity, or both, and to determine the effect of treatment on health-related quality of life, disability, dependency and death, and whether such treatments are cost effective.

Search strategy

We searched the Cochrane Stroke Group Trials Register (last searched January 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2008), MEDLINE (1950 to February 2008), EMBASE (1980 to February 2008), CINAHL (1982 to February 2008), AMED (1985 to February 2008), PsycINFO (1967 to February 2008), Digital Dissertations (1861 to March 2008), PsycBITE (searched March 2008), PEDro (searched March 2008), and British Nursing Index (1985 to March 2008). We also searched four trials registries, scanned reference lists, performed citation tracking of included trials, and contacted experts.

Selection criteria

The review author who performed the searches scrutinised all titles and abstracts, excluded irrelevant references, and obtained references for potentially relevant studies. A second review author independently scrutinised potentially relevant studies to determine whether they fulfilled inclusion criteria. We included randomised controlled trials of any intervention in patients with stroke where fatigue was a primary or secondary endpoint.

Data collection and analysis

The two review authors who scrutinised references independently extracted data. We performed a narrative review; we had intended to perform a meta-analysis but this was not possible as the interventions were too diverse for data to be combined.

Main results

We identified three trials. One randomised 83 patients with emotional disturbance after stroke to fluoxetine or placebo. After correcting for differences in fatigue severity at baseline, there was no significant difference in fatigue between groups at follow up. The second trial randomised 31 women with subarachnoid haemorrhage to tirilazad or placebo, of whom 18 were available for follow up. There was no difference in fatigue between the two groups. The third trial investigated a chronic disease self-management programme in 1150 patients with chronic diseases, of whom 125 had had a stroke. There was no difference in fatigue at follow up between the treatment and control in the subgroup with stroke.

Authors' conclusions

There is insufficient evidence available to guide the management of fatigue after stroke. Further trials are required.

PLAIN LANGUAGE SUMMARY

Interventions for post-stroke fatigue

Fatigue is common and distressing after stroke. This review found three small, randomised controlled trials that recruited a total of 239 people who had had a stroke to three different treatments (two different drug treatments and one chronic disease self-management programme). At follow up, there was no difference in fatigue levels between the patients who received the active treatments and those who received usual care or placebo. However, the trials were too small to provide firm conclusions and further trials are required.

BACKGROUND

Description of the condition

Stroke is a major cause of long-term disability. Over the past few years, evidence has been emerging that fatigue is a common, long-term problem after stroke (Ingles 1999). It is distressing to patients (van der Werf 2001), and may predict death (Glader 2002). Estimates of the prevalence of fatigue after stroke range from 16% (Glader 2002) to 70% (Carllson 2003; Leegard 1983), depending on the population studied (e.g. inpatients or community patients, time since stroke, severity of stroke), whether people with depression were included or excluded, and how fatigue was identified (e.g. single question or fatigue scales).

Normal fatigue can be defined as a state of general tiredness that is a result of overexertion and can be ameliorated by rest (De Groot 2003). Abnormal (or pathological) fatigue is a state characterised by weariness unrelated to previous exertion levels and is usually not ameliorated by rest (De Groot 2003).

Recently, diagnostic criteria and an associated structured interview have been developed to identify which stroke patients have clinically significant fatigue (Lynch 2007).

The aetiology of fatigue after stroke is uncertain. Some studies (Naess 2005; Schepers 2006; van der Werf 2001), but not all (Ingles 1999; Staub 2001), have found associations with depression. One small study found a relationship with brain stem lesions (Staub 2001), whilst others did not (Ingles 1999; Morley 2005; Naess 2005). Fatigue may have an underlying biological mechanism; one small study of 38 participants found a relationship with plasma glutamate/glutamine ratio (Syed 2007). In cancer patients, fatigue may be related to cortisol dysregulation (Bower 2005). The relationship between cortisol dysregulation and fatigue after stroke has not been studied. Another interesting hypothesis is that fatigue may be associated with physical deconditioning, which is common after stroke (Saunders 2004), but the single study which has investigated the relationship between fatigue and fitness found no association (Michael 2006).

Description of the interventions

Since fatigue following stroke may have several causative factors, there are a number of potential interventions, in combination or alone, that may help. Possible interventions include pharmacological treatments (e.g. antidepressants, stimulants), psychologi-

cal treatments (e.g. cognitive behavioural therapy, counselling) or physical treatments, such as graded exercise. It is currently not clear which approach may help to reduce the severity of fatigue following stroke. Thus, this review aimed to identify any intervention used to treat fatigue after stroke, where assessment of fatigue was a primary or secondary outcome.

How the interventions might work

Without being certain about the causes of fatigue, the mechanisms by which any intervention may work are unclear. We could hypothesise that exercise, by means of reversing physical deconditioning, might reduce fatigue; that psychological treatments might improve mood and so reduce fatigue; or that drugs, such as antidepressants, could increase levels of brain serotonin, which might, in theory, also reduce fatigue.

Why is it important to do this review?

Currently there is uncertainty about how to manage fatigue after stroke. In clinical practice, physicians may assess for co-existing, treatable conditions such as anaemia, depression, hypothyroidism and infection, but often these conditions are not present. There are currently no published systematic reviews of interventions for fatigue after stroke. Thus, this review is broad, as we wished to identify any intervention that had been used to treat fatigue after stroke, and so we decided to include trials where fatigue was a primary or secondary endpoint.

OBJECTIVES

The objectives of this systematic review were to determine:

1. whether any treatment for fatigue after stroke reduces the proportion of patients with fatigue, or the severity of fatigue, or both;

2. the effect of treatment on health-related quality of life, disability, dependency and death, and whether such treatments are cost effective.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials (RCTs) in patients with a clinical diagnosis of stroke. We included trials that compared an intervention for fatigue plus usual care versus usual care alone. We also included studies that compared the effect of different interventions, or different doses of interventions, where the interventions were aimed at treating fatigue. We included trials where fatigue was pre-specified as either a primary or secondary outcome. There were no language restrictions. We included published and unpublished trials.

Types of participants

We included adult men and women aged 18 years and over (with no upper age limit). Stroke was defined by clinical criteria, and included all pathological subtypes. We included patients with subarachnoid haemorrhage. We included any means of diagnosis or assessment of fatigue.

Types of interventions

We included any intervention used with the intention of treating fatigue as either a primary or secondary outcome, including pharmacological and non-pharmacological treatments in combination or alone. If the intervention was applied as a component of a complex intervention, the comparison was usual care alone versus usual care plus the complex intervention. We expected that the types of interventions would include antidepressants, other pharmacological agents, exercise, counselling, and cognitive behavioural therapy (CBT), but we did not limit the review to these types of interventions only.

Types of outcome measures

The primary outcome for this review was fatigue, measured either as the proportion of patients with fatigue or the severity of fatigue, or both. Examples of possible assessment measures included, but were not limited to:

- Fatigue Severity Scale (Krupp 1989);
- visual analogue scale for fatigue severity;
- fatigue self-reported questionnaire;
- energy/fatigue scale from the Medical Outcomes Study.

The secondary outcomes were health-related quality of life (assessed by, for example, Short Form 36), disability (e.g. Barthel score), dependence (e.g. Modified Rankin scale), cost effectiveness, and death.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Review Group Co-ordinator in January 2008. In addition, one of four authors (GM, EM, LS or AP) searched the following electronic databases:

- EM searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2008);
- EM searched MEDLINE (1950 to February 2008) (Appendix 1);
- EM searched EMBASE (1980 to February 2008) (Appendix 2);
- EM searched CINAHL (1982 to February 2008) (Appendix 3);
- EM searched AMED (1985 to February 2008) (Appendix 4);
- GM searched PsycINFO (1967 to February 2008) (Appendix 5);
- GM searched Digital Dissertations (1861 to March 2008);
- AP searched PEDro (The Physiotherapy Evidence Database, http://www.pedro.fhs.usyd.edu.au/) (searched March 2008);
- LS searched British Nursing Index (1985 to March 2008); and
- GM searched PsycBITE (Psychological Database for Brain Impairment Treatment Efficacy, www.psycbite.com) (searched March 2008).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we searched the following registers of ongoing trials on 3 March 2008: Current Controlled Trials (www.controlled-trials.com), Trials Central (www.trialscentral.org), and Stroke Trials Registry (www.strokecenter.org/trials/).

We used Citation tracking (Web of Science) for all included studies: GM searched for papers citing Ogden et al (Ogden 1998) and Choi-Kwon et al (Choi-Kwon 2007), and LS searched for studies citing Lorig at al (Lorig 2001).

As an additional check for ongoing studies, GM searched Health Service Research Projects in Progress (wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm) on 6 January 2009.

We searched the reference lists of included trials, observational studies and review articles about fatigue after stroke and contacted experts in the field.

Data collection and analysis

Selection of studies

All titles and abstracts from each search were scrutinised for relevance by the review author who performed the search (please see above). We excluded obviously irrelevant references and obtained full references for potentially relevant studies. A second review author scrutinised the potentially relevant studies and determined whether they fulfilled the inclusion criteria (GM scrutinised potentially relevant studies identified by EM; AP scrutinised studies identified by LS; LS scrutinised studies identified by AP; and EM scrutinised studies identified by GM). We resolved any discrepancies about whether or not the studies fulfilled the inclusion criteria by referring to the original paper and through discussion.

Contact with authors

We contacted authors of the included trials and the ongoing trials to obtain information that was not included in the trial reports, and to enquire about unpublished or ongoing trials.

Data extraction and management

Two review authors independently extracted data from the included studies and recorded the information on a data extraction form. GM and EM independently extracted data from the studies obtained from the MEDLINE and EMBASE database searches, AP and LS independently extracted data from the study identified through searching the PEDro database. We collected information regarding the age, sex and numbers of participants, the study setting, the pathological subtypes and severity of strokes included, the time since stroke onset, the intervention - including its duration, primary and secondary outcome measures, criteria used to diagnose fatigue, the assessment methods of fatigue at baseline and follow up, and the intervals at which the outcome measures were recorded.

We extracted the data onto paper forms. We had intended to use an electronic database to manage our data, but as there were only three included trials, it was more practical to manage the data using the paper forms.

Study quality

Assessment of risk of bias in included studies

We assessed the quality of studies by noting whether allocation was concealed, whether the analysis was by intention-to-treat, and whether there was blinding of outcome assessment.

For concealment of allocation, we distinguished between trials that were adequately concealed (central randomisation at a site remote from the study, computerised allocation in which records are in a locked readable file that can be assessed only after entering patient details, the drawing of opaque envelopes), inadequately concealed (open list or table of random numbers, open computer systems, drawing of non-opaque envelopes) and unclear (no information in the report or authors did not respond to our request for information or were unable to provide it).

We defined 'intention-to-treat' as present if two criteria were fulfilled: (1) all trial participants were analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities, such as ineligibility; and (2) all participants were included regardless of whether their outcomes were actually collected. For trials that did not fulfil these two criteria, we determined whether an 'available-case analysis' or a 'treatment-received analysis' had been performed.

For blinding we distinguished between trials in which the main outcome was measured by an assessor who was blind to treatment allocation, and those in which it was measured by the participants themselves or by a non-blinded assessor.

Assessment of heterogeneity

We intended to measure heterogeneity using I^2.

Measures of treatment effect

We undertook a narrative review of all studies. When trials used a number of different tools to assess fatigue, we included the main outcome measure as specified by the study authors. For instances where the study authors used a number of different outcome measures without pre-specifying the main one, we specified the main outcome measure in order of preference as follows: a dichotomous measure of fatigue designed specifically for stroke (e.g. a case definition) (Lynch 2007), a generic dichotomous measure for fatigue that has been tested in stroke, a generic dichotomous measure of fatigue not tested in stroke, a scale designed specifically for measuring fatigue severity after stroke, one of the generic fatigue scales tested in stroke (Mead 2007), a generic fatigue scale not previously tested in stroke.

If interventions included different doses (for example, high-intensity exercise versus low-intensity exercise versus control), we had intended combining the results of the various active treatment arms in a trial or, where that was not possible, we had intended to divide the control group into several parts, one to go with each active arm, so that patients were not double counted.

We intended to calculate relative risks (and 95% confidence intervals) for dichotomous outcome (i.e. fatigue or no fatigue) and standardised mean differences for continuous data, ensuring that, should some scales increase with fatigue severity whilst others decrease, we would multiply the mean values from one set of trials by -1 (or alternatively subtract the mean from the maximum possible value for the scale). We anticipated that some outcome scales would include individual questions relating to fatigue. We intended to use only the data for total scale scores, unless the individual questions had been validated as measures of fatigue.

We intended to perform pooled analyses for each intervention using the Cochrane Review Manager software, RevMan 5.0 (RevMan 2008), and using a random-effects model, but the interventions were too diverse for data to be combined.

Sub-group analysis and investigation of heterogeneity

We intended to explore heterogeneity by subgroup analyses. These were:

1. source of participants, community volunteers versus clinical patients;
2. type of treatment;
3. duration of treatment;
4. length of follow up.

We intended to use an established method for subgroup analyses (Deeks 2001).

Sensitivity analysis

We intended to explore methodological heterogeneity through the use of sensitivity analysis.

1. Allocation concealment: we intended to re-analyse the data including only those trials with adequate allocation concealment.
2. Intention-to-treat analysis: we intended to re-analyse the data including only those trials with intention-to-treat analyses.
3. Blinding of outcome assessment: we intended to re-analyse the data including only those trials with blinding of outcome assessment.
4. Publication type (peer-reviewed journal, conference abstract/proceedings, doctoral dissertation): we intended to re-analyse the data including only those trials from peer-reviewed journals.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of search

One review author (EM) scrutinised 4231 titles and another review author (GM) scrutinised 241 titles. Between them, both authors retrieved 17 full papers. Of these 17 papers, there was one obviously irrelevant randomised controlled trial (RCT) (eperisone versus physiotherapy for muscle tone), one case report, seven observational studies, six (non-systematic) review articles, and two RCTs which met our inclusion criteria (Choi-Kwon 2007; Ogden 1998).

Another review author (LS) scrutinised 83 titles and retrieved seven full papers including five reviews and two obviously irrelevant RCTs. This author scrutinised a further 355 titles identified from citation searching.

A fourth review author (AP) scrutinised 187 titles and retrieved five full papers. Of these, two were obviously irrelevant and three

were initially considered to be possibly relevant but after further discussion, two were excluded (Allison 2007; Underwood 2006), leaving one RCT that met our inclusion criteria (Lorig 2001).
One review author (GM) identified one ongoing RCT by searching trials registers (SATS 2004) and another review author (EM) identified one ongoing RCT by contacting Gunnel Carllson (COGRAT 2008).

Included studies

Three completed trials met our inclusion criteria.
Choi Kwon et al evaluated the therapeutic effect of fluoxetine on fatigue and other emotional disturbances in a placebo controlled, double-blind trial in 83 outpatients with post-stroke emotional disturbances at a mean of 14 months after stroke onset (Choi-Kwon 2007). The presence of fatigue or the severity of fatigue were not selection criteria for inclusion in the study. Participants were assigned to receive either 20 mg of fluoxetine a day or placebo for three months. Post-stroke fatigue was evaluated by the fatigue severity scale (FSS) and visual analogue scale (VAS) at baseline, three months and six months after the start of treatment. There were two primary endpoints: the mean VAS scores and the mean FSS scores. The secondary endpoints were the per cent changes in VAS scores and FSS scores between baseline and follow up. The participants' mean age was 56.4 years in the placebo arm and 57.2 years in the drug-treated arm. Diagnoses included both ischaemic and haemorrhagic strokes.
Ogden et al assessed the effectiveness of giving tirilazad mesylate (a hypothesised neuroprotective agent), in women with subarachnoid haemorrhage on neuropsychological and psychosocial outcomes including fatigue (Ogden 1998). Thirty-one participants were randomly assigned to receive either 100 ml of placebo (vehicle, i.e. the substance in which a drug is administered) or 100 ml of 1.5 mg/ml tirilazad mesylate for 10 consecutive days after subarachnoid haemorrhage. The presence of fatigue was not recorded at baseline. Of these 31 participants, 18 were still alive and were capable of, and consented to, being interviewed three months later. This interview included a two-hour battery of neuropsychological tests, a semi-structured interview and a questionnaire performed by a neurosurgeon. In the semi-structured interview, participants were asked whether they were suffering from fatigue or sleepiness that was much worse than before their subarachnoid haemorrhage - if they answered 'yes' then the interviewer explored this with further questioning and participants were asked to provide specific examples. Participants' responses to questioning were analysed as a 'yes or no' to debilitating fatigue based on a subjective opinion of the interviewer. The mean age of participants was 45.1 years for the drug-treated group and 49.7 for the placebo arm.
Lorig et al evaluated a chronic disease self-management programme (CDSMP) on health status, health care utilisation and self-efficacy outcomes (Lorig 2001). The trial recruited 1140 community-dwelling participants with a mean age of 65 years from various forms of public advertising over a four-and-a-half-year period. Participants had diagnoses of chronic lung disease, heart disease, stroke ('completed cerebrovascular accident with neurologic handicap and normal mentation') or chronic arthritis. Participants were sent a questionnaire at baseline and randomly assigned to immediate CDSMP or were put on a waiting list to receive CDSMP after the six-month follow-up assessments ('wait-list' control group). There were 125 patients in the subgroup with stroke, of whom 67 were allocated to CDSMP and 58 to 'wait list' control. Patients allocated immediate CDSMP participated in seven weekly sessions, each lasting two-and-a half hours, in community centres where they were taught CDSMP by peer leaders. This included teaching about exercise programmes, the use of cognitive symptom management techniques, nutritional change, fatigue and sleep management, use of community resources, use of medications, dealing with emotions of fear, anger and depression, communication with others, problem solving, and decision making. The programme was implemented through a 'self efficacy theory', the process of which was documented in a manual, and all the participants received a 'Living a Healthy Life with Chronic Conditions' publication with the course content outlined to serve as a guide. Six months after recruitment, all 'wait list' control patients were offered the CDSMP; of these, 72% accepted the CDSMP. Data were collected at baseline and at six months, using a questionnaire. This enabled the researchers to compare six-month outcomes in the patients allocated immediate CDSMP and those allocated 'wait list control'. Primary outcomes were 'health behaviours, health status, and health service utilisation'. The energy/fatigue scale from the Medical Outcomes Study scale was used to measure fatigue. Then, to explore the long-term effects of CDSMP, outcome data were collected at one and two years from the participants allocated immediate CDSMP and from those 'wait list control' participants who accepted the CDSMP at six months. The purpose of this longitudinal element of the study was to describe the changes to participants from baseline, to examine the extent to which initial levels of self-efficacy and changes in self-efficacy were associated with reductions in healthcare utilisation and to describe the cost of the CDSMP intervention and potential savings due to changes in healthcare utilisation. The trial did not report results separately for the different chronic diseases (Lorig 2001). The authors of the trial provided unpublished data for the subgroup of 125 patients with stroke at the six-month follow-up, which compared outcomes between the CDSMP group and the 'wait list' control.

Ongoing studies

We identified two ongoing RCTs. The Sleep Apnoea Treatment after Stroke trial is randomising people with sleep-disordered breathing after stroke to continuous positive airways pressure (CPAP) or sham CPAP (SATS 2004). The fatigue severity score is a secondary endpoint.

The cognitive and graded activity training trial on post-stroke fatigue (COGRAT 2008) is an ongoing multi-centre, randomised controlled trial comparing 'cognitive treatment' alone versus graded activity and cognitive treatment in patients who are at least four months post stroke and who have a fatigue score of more than 40 as measured by the Checklist for Individual Strength (Vercoulen 1994). Ninety-six participants will be randomised. Fatigue is an outcome measure.

Excluded studies

From the PEDro search, we excluded a trial of standing practice (Allison 2007), as there were no fatigue-related outcomes. We excluded a trial of constraint-induced movement therapy (Underwood 2006), because the intervention was not aimed at treating fatigue.

Risk of bias in included studies

Allocation

Choi Kwon et al randomised patients who fulfilled the trial inclusion criteria (i.e. post-stroke emotional disturbance) using a computer-generated list of treatment numbers (Choi-Kwon 2007). The presence or severity of fatigue were not criteria for selection for the study; consequently, the placebo group contained a significantly higher number of patients with post-stroke fatigue at baseline than the treatment arm.

Ogden at al stated that there was allocation concealment but details of the randomisation methods are not available (Ogden 1998).

The participants in the trial by Lorig et al underwent a serial randomisation process whereby for each site, a randomisation ratio was determined to ensure that there were between 10 and 15 patients in the treatment arm (Lorig 2001). This ratio differed between sites. Allocation concealment was not reported in the study methods.

Blinding

In one trial (Choi-Kwon 2007), participants and providers of the intervention were blinded to the treatment allocation. Fatigue was measured by self-report. In the second trial (Ogden 1998), participants, providers and outcome assessors were blinded to treatment allocation. In the third trial (Lorig 2001), the participants and providers were aware of the assigned interventions. The outcomes were reported by participants aware of their interventions by self-reported questionnaires (i.e. unblinded). Data collection from the questionnaires was conducted by people blinded to the intervention.

Intention-to-treat analysis

Choi-Kwon et al reported that intention-to-treat analysis was performed, but did not provide data on how many participants, if any, dropped out (Choi-Kwon 2007). Ogden et al did not perform intention-to-treat analysis as fatigue data could not be obtained from patients who had died, those who were deemed incapable of participating and those who did not consent (Ogden 1998). We classified this as 'an available-case analysis'. In the third trial (Lorig 2001), six-month follow-up data were available for 104 of the subgroup of 125 stroke patients who were recruited, so we classified this as an 'available-case analysis'.

Effects of interventions

We could not perform meta-analysis as the interventions were too dissimilar.

Choi-Kwon et al concluded that fluoxetine was ineffective in treating fatigue after stroke (Choi-Kwon 2007). The mean FSS in the placebo group (43 participants) and the fluoxetine group (40 participants) at baseline were 4.7 and 4.8 respectively, and the mean VAS was 6.0 and 4.8 respectively, indicating significantly higher levels of fatigue in the placebo group at baseline. At three months, the mean FSS in the placebo and fluoxetine groups were 4.3 and 3.7 respectively and the mean VAS scores were 5.3 and 4.3 respectively. At six months, the mean FSS in the placebo and fluoxetine groups were 4.2 and 3.6 respectively and mean VAS scores were 5.5 and 4.4 respectively. The percentage change in the VAS and FSS scores from baseline to follow-up assessments were not significantly different between the fluoxetine and placebo groups. It was noted that the total number of patients reporting fatigue in the fluoxetine group fell from 40 to 33 compared with 43 to 40 in the control group at three months.

Ogden et al reported that only four out of nine participants in the tirilazad mesylate arm complained of debilitating fatigue at three months compared with all nine participants in the placebo arm (Ogden 1998). The difference between the two groups was statistically significant.

Lorig et al demonstrated that CDSMP was a feasible intervention that was significantly better than 'wait list' control at six months in terms of health status and hospitalisations for all the 1140 patients randomised (Lorig 2001). At baseline there were 125 participants with stroke as their primary chronic condition (58 controls and 67 interventions). The mean for the 125 patients on the energy-fatigue scale was 2.08 (standard deviation (SD) = 1.03) at baseline (1 to 5 range). Of the 125 patients, 104 (83%) completed six-month questionnaires (46 'wait list' control and 58 treatment). The mean changes scores were 0.246 (SD = 0.600) for controls and 0.087 (SD = 0.988) for treatment (i.e. fatigue became worse for 'wait list' controls but remained almost unchanged for CDSMP participants). The difference was not significant (P value 0.253).

DISCUSSION

Summary of main results

To our knowledge, this is the first systematic review of interventions for fatigue after stroke. We identified only three published trials and two ongoing trials. Of the three published trials, fatigue was a secondary endpoint and the participants did not have to have fatigue to be included in the study. One trial found no difference between the effect of fluoxetine or placebo on fatigue (Choi-Kwon 2007). The second trial found that patients with subarachnoid haemorrhage were less likely to have fatigue at three months if they had received tirilazad mesylate, but this trial was very small and more than half of the patients randomised were not available for follow up (Ogden 1998). The third trial, which recruited 1140 patients with a variety of different chronic diseases, found that a chronic disease self-management programme was no more effective in reducing fatigue than a 'wait list control' group for the subgroup of 125 people after stroke (Lorig 2001).

One ongoing trial is recruiting patients who have fatigue after stroke (COGRAT 2008). The primary outcome measure is fatigue. This trial is designed to determine whether cognitive treatment plus graded activity is more effective than cognitive treatment alone. There is no 'usual care' arm in this trial, and so it will not be able to test the hypothesis that cognitive treatment is better than usual care. This hypothesis would be worth testing, because one observational study demonstrated an association between fatigue and reduced 'locus of control' (Schepers 2006). The second ongoing trial is investigating CPAP in sleep-disordered breathing and will report fatigue as a secondary endpoint. It is unlikely that CPAP would be a widely applicable treatment for fatigue after stroke, unless it was associated with sleep-disordered breathing and the patient was able to comply with treatment.

Consequently, uncertainties remain about whether any of the interventions we identified might be effective for fatigue after stroke.

Overall completeness and applicability of evidence

Our review was deliberately broad and we sought to include trials in which fatigue was a secondary as well as a primary endpoint, so that the review would inform future research. The trials we identified are relevant to our review question, although the patients in the three completed trials did not have to have fatigue at baseline to be eligible for inclusion, and so the trials are not directly relevant to people presenting with fatigue after stroke. One ongoing trial is recruiting patients with fatigue after stroke and comparing graded activity plus cognitive treatment versus cognitive treatment alone (COGRAT 2008).

The studies we identified do not address all of the objectives of the review sufficiently; in particular, further research is required to test other, potentially effective interventions such as cognitive therapy, and to investigate the effect of the interventions on relevant outcomes such as health-related quality of life, costs, and risks.

Quality of evidence

We cannot draw robust conclusions as we identified only three completed studies, providing data on a total of 226 patients, and using three different interventions. There were methodological limitations with all three trials.

Potential biases in the review process

We attempted to limit bias in the review process. This review incorporated extensive literature searches guided by the Cochrane Stroke Group and we sought unpublished and ongoing work through contact with authors of included studies and other experts in the field. Two review authors independently decided whether studies should be included, and data were extracted independently by two review authors.

Agreements and disagreements with other studies and reviews

As far as we know, there are no other systematic reviews of interventions for post-stroke fatigue. We found only three trials that fulfilled our wide inclusion criteria, and these could not be combined in a meta-analysis. Our findings are consistent with previously published papers calling for more research to determine the effectiveness of interventions for post-stroke fatigue.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is insufficient evidence to guide practice in treating fatigue following stroke.

Implications for research

Given the high prevalence of fatigue following stroke, more research is urgently needed to identify treatment for this common and distressing symptom. As a first step, further work could usefully be done to explore associations of fatigue after stroke, which might provide targets for treatment. This would include systematic reviews of observational studies. Given that some studies have found an association between fatigue and mood disorders, the develop of a cognitive intervention might also be a logical step forward.

ACKNOWLEDGEMENTS

We are very grateful to Brenda Thomas and Hazel Fraser of the Cochrane Stroke Group who helped develop the search strategies, searched the Cochrane Stroke Group Trials Register and the Cochrane Central Register of Controlled Trials. We are grateful to the editors and peer reviewers for their helpful comments on the review (Professor Peter Langhorne, Professor Anne Forster, Dr Valery Feigin, Dr Steff Lewis, Mrs Brenda Thomas). Ms Maureen Harding, Geriatric Medicine, University of Edinburgh, helped obtain articles. The Scottish Branch of the British Geriatrics Society provided a small project grant to Dr McGeough to support this work.

Professor Kate Lorig and Dr Phil Ritter, Stanford University, accessed and provided data from the subgroup of stroke patients from the Lorig 2001 trial. Gunnel Carllson responded to our queries about ongoing trials. Professor Fasotti and Dr Zelditz provided information about COGRAT 2008, and Dr Brown provided information about SATS 2004.

The work presented here represents the views of the authors and not necessarily those of the funding bodies.

REFERENCES

References to studies included in this review

Choi-Kwon 2007 *{published data only}*
Choi-Kwon S, Choi J, Kang D-W, Kim JS. Fluoxetine is not effective in the treatment of post-stroke fatigue: a double-blind, placebo-controlled study. *Cerebrovascular Diseases* 2007;**23**:102–8.

Lorig 2001 *{published data only}*
Lorig KR, Ritter P, Stewart AL, Sobel DS, Brown BW, Bandura A, et al.Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Medical Care* 2001;**39** (11):1217-23.

Ogden 1998 *{published data only}*
Ogden JA, Mee EW, Utley T. Too little, too late: does tirilazad mesylate reduce fatigue after subarachnoid haemorrhage?. *Neurosurgery* 1998;**4**:782–7.

References to studies excluded from this review

Allison 2007 *{published data only}*
Allison R, Dennett R. Pilot randomized controlled trial to assess the impact of additional supported standing practice on functional ability post stroke. *Clinical Rehabilitation* 2007;**21**(7):614–9.

Underwood 2006 *{published data only}*
Underwood J, Clark PC, Blanton S, Aycock DM, Wolf SL. Pain, fatigue, and intensity of practice in people with stroke who are receiving constraint-induced movement therapy. *Physical Therapy* 2006;**86**(9):1241–50.

References to ongoing studies

COGRAT 2008 *{unpublished data only}*
Fasotti L. Effectiveness of cognitive and graded activity training (COGRAT) on post stroke fatigue. A multi-center study. http://www.onderzoekinformatie.nl/en/oi/nod/onderzoek/OND1326577/.

SATS 2004 *{unpublished data only}*
Brown D. SATS. Sleep Apnea Treatment after Stroke. Stroke Trials Directory, Internet Stroke Center: www.strokecenter.org/trials/.

Additional references

Bower 2005
Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2005;**30**:92–100.

Carllson 2003
Carllson GE, Mooler A, Blomstrand C. Consequences of mild stroke in persons < 75 years: a 1 year follow up. *Cerebrovascular Diseases* 2003;**16**:383–8.

De Groot 2003
De Groot MH, Phillips SJ, Eskes GA. Fatigue associated with stroke and other neurological conditions: implications for stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation* 2003;**84**:1714–20.

Deeks 2001
Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining resuls from several studies in meta-analysis. In: Egger M, Davey-SMith G, Altman DG editor

(s). *Systematic reviews in healthcare: Meta-analysis in context*. 2nd Edition. London: BMJ Publishing Group, 2001.

Glader 2002
Glader E-L, Stegmayr B, Asplund K. Post-stroke fatigue. A 2-year follow-up study of stroke patients in Sweden. *Stroke* 2002;**33**: 1327–33.

Ingles 1999
Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Archives of Physical Medicine and Rehabilitation* 1999;**80**:173–8.

Krupp 1989
Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale . *Archives of Neurology* 1989;**46**:1121–3.

Leegard 1983
Leegard OF. Diffuse cerebral symptoms in convalescents from cerebral infarction and myocardial infarction. *Acta Neurologica Scandinavica* 1983;**67**:348–55.

Lynch 2007
Lynch J, Mead G, Greig C, Young A, Lewis S, Sharpe M. Fatigue after stroke: the development and evaluation of a case definition. *Journal of Psychosomatic Research* 2007;**63**:539–44.

Mead 2007
Mead G, Lynch J, Greig C, Young A, Lewis S, Sharpe M. Evaluation of fatigue scales in stroke patients. *Stroke* 2007;**38**:2090–5.

Michael 2006
Michael KM, Allen JK, Macko RF. Fatigue after stroke: relationship to mobility, fitness, ambulatory activity, social support and falls efficacy. *Rehabilitation Nursing* 2006;**5**:210–7.

Morley 2005
Morley W, Jackson K, Mead G. Fatigue after stroke: neglected but important. *Age and Ageing* 2005;**34**:313.

Naess 2005
Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr K-M. Fatigue at long-term follow-up in young adults with cerebral infarction. *Cerebrovascular Diseases* 2005;**20**:245–50.

RevMan 2008
The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

Saunders 2004
Saunders DH, Greig CA, Young A, Mead GE. Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [Art. No.: CD003316. DOI: 10.1002/14651858.CD003316.pub2]

Schepers 2006
Schepers VP, Visser-Meily AM, Ketelaar M, Lindeman E. Post-stroke fatigue: course and its relationship to personal and stroke-related factors. *Archives of Physical Medicine and Rehabilitation* 2006;**87**:184–8.

Staub 2001
Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovascular Diseases* 2001;**12**:75–81.

Syed 2007
Syed AB, Castell LM, Ng A, Winward C, Rothwell PM. Plasma glutamate levels predict fatigue after TIA and minor stroke. *Cerebrovascular Diseases* 2007;**23 Suppl 2**:117.

van der Werf 2001
van der Werf SP, van den Broek HL, Anten HS, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *European Neurology* 2001;**45**:28–33.

Vercoulen 1994
Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research* 1994;**38**: 383–92.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Choi-Kwon 2007

Methods	Double-blind, placebo-controlled trial of fluoxetine Presence or severity of fatigue were not used as a selection criterion for entry into the trial
Participants	83 outpatients with post-stroke emotional disturbance at a mean of 14 months after stroke onset Haemorrhagic and ischaemic stroke included
Interventions	Fluoxetine 20 mg or placebo daily for 3 months
Outcomes	Primary outcomes: fatigue severity scale and visual analogue scale Secondary outcomes: percent changes in FSS and VAS scores between baseline and follow up
Notes	Patients did not have to have fatigue to be included; consequently, the placebo group contained a significantly higher number of patients with post-stroke fatigue at baseline compared with the treatment arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Computer-generated list of treatment numbers

Lorig 2001

Methods	Randomised controlled trial
Participants	1140 community-dwelling patients with diagnoses of chronic lung disease, heart disease, stroke ('completed cerebrovascular accident with neurologic handicap and normal mentation')or chronic arthritis were recruited Data for the 125 patients with stroke were provided by the authors of the trial
Interventions	Chronic disease self-management programme (CDSMP) Active intervention: 7 weekly sessions each lasting 2.5 hours in community centres where patients were taught CDSMP by peer leaders. This included teaching about exercise programmes, the use of cognitive symptom management techniques, nutritional change, fatigue and sleep management, use of community resources, use of medications, dealing with emotions of fear, anger and depression, communication with others, problem solving, and decision making. The programme was implemented through a 'self-efficacy theory', the process of which was documented in a manual, and all the participants received a 'Living a Healthy Life with Chronic Conditions' publication with the course content outlined to serve as a guide Control arm: a 'wait list control'. Patients continued with usual care for 6 months and were then offered the CDSMP
Outcomes	Primary outcomes: 'health behaviours, health status, and health service utilisation' The energy/fatigue scale from the Medical Outcomes Study was used to measure fatigue The 6-month follow-up data from the 125 patients with stroke were provided by the authors of the trial to allow us to compare the effect of the CDSMP with the 'wait list' control

Lorig 2001 (*Continued*)

Notes	

Ogden 1998

Methods	Randomised controlled trial
Participants	Women with subarachnoid haemorrhage
Interventions	100 ml of vehicle (placebo) or 100 ml of 1.5 mg/ml tirilazad mesylate for 10 consecutive days after onset of subarachnoid haemorrhage
Outcomes	Neuropsychological outcomes at 3 months A diagnosis of fatigue at 3 months was based on the interviewer's subjective opinion
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	The publication states that there was allocation concealment but no details were available from either the publication or the authors

FSS: fatigue severity scale
VAS: visual analogue scale

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

Allison 2007	No fatigue outcomes
Underwood 2006	Intervention not aimed at treating fatigue

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

COGRAT 2008

Trial name or title	Cognitive and graded activity training
Methods	Multi-centre, randomised controlled trial
Participants	Patients who are at least 4 months post-stroke and who have a fatigue score of > 40 as measured by the Checklist for Individual Strength
Interventions	Cognitive treatment alone versus cognitive treatment plus an individually designed graded physical activity programme The physical activity programme is based on the Exercise Programming Recommendations for Stroke Survivors of the American Heart Association The cognitive treatment will include cognitive and behavioural strategies aimed at dealing with fatigue, delivered to groups of a maximum of 4 people
Outcomes	Fatigue complaints lists, registrations of physical activity (with actometers), neuropsychological tests, and psychosocial questionnaires on coping, attributions, self-efficacy, and social support at end of treatment and 6 months after the end of treatment
Starting date	April 2007
Contact information	Professor Dr L Fasotti Email: l.fasotti@smk-research.nl http://www.nici.ru.nl
Notes	96 patients will be randomised

SATS 2004

Trial name or title	The Sleep Apnoea Treatment after Stroke trial
Methods	Randomised, double-blind (patient, investigator), placebo-controlled trial
Participants	Ischaemic stroke within 7 days of planned polysomnography, modified Rankin Scale score > 1 Anticipated recruitment is 200
Interventions	Active intervention: continuous positive airways pressure (CPAP) via nasal mask during sleep Control: sham CPAP
Outcomes	Primary outcome measure: (1) hours of treatment use per week, (2) number of patients who withdraw from study (Time frame: 3 months) Secondary outcome measures include functional outcome, depression, fatigue, and sleepiness
Starting date	September 2004

SATS 2004 (*Continued*)

Contact information	Devin Brown, MD, MS Assistant Professor, Stroke Program, University of Michigan Tel: +1 734 936 9075
Notes	End date: December 2010 ClinicalTrials.gov identifier: NCT00282815

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

We used the following search strategy for MEDLINE and adapted it for the other databases.

1. cerebrovascular disorders/or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/or exp "Intracranial Embolism and Thrombosis"/or exp intracranial hemorrhages/or vasospasm, intracranial/or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. fatigue/ or fatigue syndrome, chronic/ or asthenia/ or mental fatigue/ or muscle fatigue/ or lethargy/
9. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.
10. ((low or lack) adj5 energy).tw.
11. 8 or 9 or 10
12. 7 and 11

Appendix 2. EMBASE search strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or exp carotid artery disease/ or exp brain hematoma/ or exp brain hemorrhage/or exp brain infarction/or exp brain ischemia/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/
2. stroke unit/ or stroke patient/
3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or aploplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
6. hemiplegia/or paresis/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. fatigue/ or chronic fatigue syndrome/ or exhaustion/or lassitude/or muscle fatigue/
10. lethargy/ or listlessness/or malaise/ or apathy/ or dysthymia/or asthenia/ or neurasthenia/
11. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.
12. ((low or lack) adj5 energy).tw.
13. 9 or 10 or 11 or 12
14. 8 and 13

15. limit 14 to human
16. (hepatitis or dialysis or cancer or carcinoma or meningitis or heat stroke or cerebral palsy).ti.
17. (parkinson$ or sclerosis or myeloma or tumor$ or tumour$ or transplant$).ti.
18. exp neoplasm/
19. (kidney or renal or heat or cardiac or migrane).ti.
20. 16 or 17 or 18 or 19
21. 15 not 20

Appendix 3. CINAHL search strategy

1. cerebrovascular disorders/or exp carotid artery diseases/ or cerebral aneurysm/ or "cerebral embolism and thrombosis"/or exp cerebral ischemia/ or cerebral vascular accident/ or cerebral vasospasm/or exp intracranial hemorrhage/or vertebral artery dissections/
2. stroke patients/ or stroke units/
3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
6. hemiplegia/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. fatigue/ or fatigue syndrome, chronic/ or "fatigue (SABA CCC)"/ or "fatigue (NANDA)"/ or muscle fatigue/ or asthenia/
10. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.
11. ((low or lack) adj5 energy).tw.
12. 9 or 10 or 11
13. 8 and 12

Appendix 4. AMED search strategy

1. cerebrovascular disorders/or cerebral hemorrhage/or cerebral infarction/or cerebral ischemia/ or cerebrovascular accident/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplexy$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or bleed$)).tw.
5. hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 0r 2 or 3 or 4 or 5 or 6
8. fatigue/ or fatigue mental/ or fatigue syndrome chronic/ or muscle fatigue/
9. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.
10. ((low or lack) adj5 energy).tw.
11. 8 or 9 or 10
12. 7 and 11

Appendix 5. PsycInfo search strategy

1. cerebrovascular disorders/or cerebral hemorrhage/or cerebral ischemia/ or cerebrovascular accidents/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. fatigue/ or chronic fatigue syndrome/ or hypersomnia/or sleepiness/or asthenia/ or neurasthenia/or apathy/ or dysthymic disorder/
9. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw.
10. ((low or lack) adj5 energy).tw.
11. 8 or 9 or 10
12. 7 and 11

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 3, 2009

9 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Gillian Mead, Martin Dennis, Michael Sharpe and Susan Lewis wrote the protocol.

Elizabeth McGeough, Gillian Mead, Alex Pollock and Lorraine Smith performed the searches, selected studies fulfilling the inclusion criteria and extracted data. Susan Lewis provided advice on statistical analysis and interpretation. Elizabeth McGeough and Gillian Mead drafted the review, all authors edited the review and all approved the final version.

DECLARATIONS OF INTEREST

Michael Sharpe has received a research grant from the Scottish Government Chief Scientist Office to carry out research on a related topic.

Gillian Mead has been awarded a project grant from the Scottish Government Chief Scientist Office to perform a longitudinal study of fatigue after stroke. The preliminary results of this Cochrane review were used in the application for funding to justify the need for further studies in this area.

SOURCES OF SUPPORT

Internal sources

- Nursing & Health Care, Faculty of Medicine, University of Glasgow, UK.

(Lorraine Smith)

- NHS Lothian, UK.

(Gillian Mead, Martin Dennis, Susan Lewis)

- University of Edinburgh, UK.

(Gillian Mead, Martin Dennis, Susan Lewis, Michael Sharpe)

- South East Scotland Postgraduate Training in Geriatric Medicine, UK.

(Elizabeth McGeough)

- Nursing, Midwifery and Allied Health Professions Research Unit, Glasgow Caledonian University, UK.

(Alex Pollock)

- Chief Scientist Office, Scottish Government, UK.

(Alex Pollock)

External sources

- Scottish Branch of the British Geriatrics Society, UK.

Small project grant to Elizabeth McGeough for searches and retrieval of articles

INDEX TERMS

Medical Subject Headings (MeSH)

Fatigue [etiology; *therapy]; Randomized Controlled Trials as Topic; Stroke [*complications; psychology]

MeSH check words

Female; Humans; Male