CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

MOOD, COGNITION AND FATIGUE FOLLOWING STROKE

EVIDENCE TABLES

Post-Stroke Fatigue

Update 2019

Lanctôt KL, Swartz RH (Writing Group Chairs) on Behalf of the Canadian Stroke Best Practice Recommendations Mood, Cognition and Fatigue following Stroke Writing Group and the Canadian Stroke Best Practice and Quality Advisory Committee, in collaboration with the Canadian Stroke Consortium

Table of Contents

Search Strategy 3

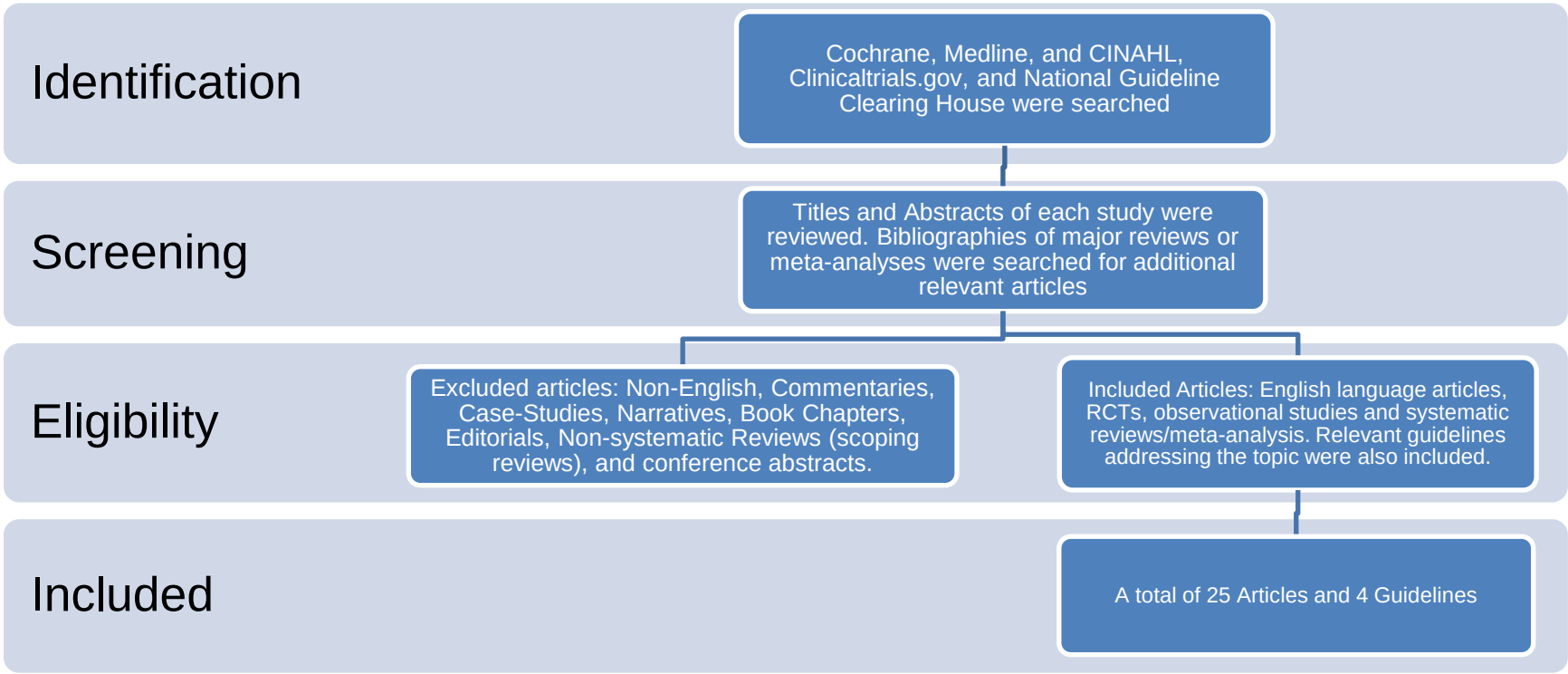
Published Guidelines.....4

Incidence and Risk Factors for the Development of Post-Stroke Fatigue 6

Treatment for Post-Stroke Fatigue 11

Reference List 16

Search Strategy



The Medline, Embase, PsycINFO, and Cochrane databases were searched using the terms [stroke OR cerebrovascular disorders] AND [Fatigue]. Titles and abstracts were reviewed for relevance, followed by a full text review of selected articles. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 24 articles and 4 guidelines were included.

Published Guidelines

Guideline	Recommendations
Hinkle JL, Becker KJ, Kim JS, Choi-Kwon S, Saban KL, McNair N, Mead GE; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing and Stroke Council. **Poststroke fatigue: Emerging evidence and approaches to management: A scientific statement for healthcare professionals from the American Heart Association.** ***Stroke* 2017; Jul;48(7):e159-e170**	The scientific statement provides an international perspective on the emerging evidence surrounding the incidence, prevalence, quality of life, and complex pathogenesis of poststroke fatigue. Evidence for pharmacological and nonpharmacological interventions for management are reviewed, as well as the effects of poststroke fatigue on both stroke survivors and caregivers.
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. **Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;47:e98–e169.**	None
Intercollegiate Stroke Working Party. National clinical guideline for stroke, *5th* Edition. London: Royal College of Physicians, 2016.	People with stroke who are medically stable but who report fatigue should be offered an assessment for mental and physical factors that may be contributing, particularly when engagement with rehabilitation or quality of life is affected. People with fatigue after stroke and their family/carers should be given information, reassurance and support to identify their personal indicators and triggers for fatigue and supported to develop strategies to anticipate and manage fatigue.
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 Jun. p.p. 42-43	4.14 Patients with post-stroke fatigue should be screened for depression There is insufficient evidence to recommend interventions for management of post-stroke fatigue, including**:** fluoxetine, tirilizad, a chronic disease self-management programme or modafinil
Management of Stroke Rehabilitation Working Group. VA/DoD clinical practice guideline for the management of stroke rehabilitation. Washington (DC): Veterans Health Administration, Department of Defense; 2010. p.80-98	None

Guideline	Recommendations
Rehabilitation. In: Clinical guidelines for stroke management 2010. Melbourne (Australia): National Stroke Foundation; 2010 Sep. p. p.104.	Therapy for stroke survivors with fatigue should be organized for periods of the day when they are most alert. **(GPP)** Stroke survivors and carers/families should be provided with information and education about fatigue including potential management strategies such as exercise, establishing good sleep patterns, and avoidance of sedating drugs and excessive alcohol. **(GPP)**

Evidence Tables

Incidence and Risk Factors for the Development of Post-Stroke Fatigue

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cumming et al. 2016 **Australia** **Systematic Review**	NA	49 studies (n =7,475) which measured fatigue using a dedicated fatigue scale at any time post-stroke. Intervention studies were included if baseline (pre-intervention) fatigue data were available.	Pooling of results from studies using similar fatigue scales and cut-off points	Prevalence of fatigue	17 different fatigue scales were used. The most commonly reported scale was the Fatigue Severity Scale (FSS) (n=24). In these studies, the mean time of reporting since stroke ranged from 4.6 days to 6 years. There were sufficient data to pool data for 2 fatigue scales Using the results from 22 studies that used the FSS and a cut-off level of ≥4 or >4, the prevalence of post-stroke fatigue was 50%, 95% CI 43–57%. Estimates of fatigue were stable across time (within 3 months of stroke 55%, 95% CI 25–85%; 1-6 months 46%, 95% CI 31–62%; and >6 months 53%, 95% CI 48–58%) Using the results from 4 studies that used the Multidimensional Fatigue Inventory (MFI) General sub scale with a cut-off level of ≥12 or >12, the prevalence of post-stroke fatigue was 56%, 95% CI 51-62%.
Elf et al. 2016 **Sweden** **Cross-sectional study**	NA	102 of 349 patients diagnosed with stroke who were admitted to stroke units from 2006-2007, included in the "Life After Stroke Phase 1", who were available for follow-up at 6 years. Mean age was 62 years, 56% were male.	All information was collected by interview in the participant's homes.	**Primary outcome:** Presence of fatigue, identified by a score of ≥4 using the Fatigue Severity Scale 7-item version **Secondary outcomes:** Stroke Impact Scale (SIS), Hospital Anxiety and Depression Scale	At 6 years, 37% of patients reported fatigue. Persons with fatigue were more likely to have suffered a moderate to severe stroke, had lower scores on many domains of the SIS and demonstrates signs of anxiety and depression, compared with persons who did not report fatigue.
Duncan et al. 2012 **UK** **Systematic Review**	NA	9 observational studies (n=959) including persons who were recruited prospectively within the first 6 months of stroke, and in which an assessment of post-stroke fatigue was conducted using a standardized scale at two or more time points. Mean age of participants ranged from 45-73 years.	Narrative synthesis of data	**Primary outcome:** Frequency of fatigue	The frequency of fatigue at first assessment (10 days to 6 months) ranged from 35% to 92% across studies. The frequency of fatigue at final assessment (6-24 months) ranged from 33% to 86%) 7 studies reported that the frequency of fatigue declined from the first to second assessment, whereas 2 studies reported an increase in fatigue frequency over time.
Naess et al. 2012	NA	328 of 541 patients admitted to hospital following acute	Surviving patients received a postal questionnaire >6	**Primary outcomes:** Pain (10-point VAS), fatigue	141 (46%) patients reported fatigue. The mean ± sd FSS score was 4.4±1.8

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **Prospective study**		ischemic stroke, included in the Bergen Stroke Study, who were available for follow-up 372 days post stroke. Mean age was 67.7 years.	months following stroke.	(Fatigue Severity Scale) and depression (Hospital Anxiety & Depression Scale, depression component). FSS score ≥5 indicated fatigue.	157 (48%) patients reported pain (VAS score>0) 61 (19%) patients reported being depressed Pain and depression were correlated with fatigue scores.
Parks et al. 2012 **Canada** **Prospective study**	NA	228 persons available for 1-year follow-up from the Stroke Outcomes Study cohort (n=522). Mean age was 68 years, 53% were male.	Trained stroke assessors conducted interviews with participants to evaluate function, quality of life, depression, and fatigue.	**Primary outcome:** Presence and severity of post stroke fatigue, assessed with the Fatigue Impact Scale (FIS).	36.8% (n=84) of respondents reported experiencing fatigue at least once per month and, of these participants, 59.5% reported that fatigue was one of the worst (n=34) or the worst (n=16) symptom they experienced. Younger age at the time of stroke was significantly associated with increased frequency ($p<0.05$) and duration ($p<0.01$) of fatigue as well as disability attributed to fatigue ($p<0.01$) and the ranking of fatigue as a post-stroke symptom ($p<0.01$). Younger age was also significantly associated with a greater impact of fatigue on cognitive ($p<0.05$) and psychosocial function ($p<0.05$).
Van Eijsden et al. 2012 **Netherlands** **Retrospective study**	NA	250 patients, aged ≥18 years, with the ability to walk at least 10 metres without assistance, who were cognitively intact and where discharge destination was home. Mean age was 57.1 years, 65% were male.	Development of a model to predict post-stroke fatigue, defined as an increase of 1.41 points on the Fatigue Severity Scale. Potential factors included personal factors, (age, sex, marital status, physical activity, pre-stroke comorbidity) stroke characteristics, (type of stroke, lateralization, time since stroke onset, and history of previous stroke) physical function, (strength and balance) cognitive function, emotional function (depression and anxiety, fear of falling) and activities and participation (gait performance ADL and EADL).	**Primary outcome:** Prevalence of fatigue, identified as a total score of ≥4 points using the Fatigue Severity Scale (FSS). Assessments were conducted at time of discharge from hospital (mean time since stroke was 97 days) and 24 weeks later.	Data from 242 patients were available at 24 weeks. Fatigue was reported at baseline and 24 weeks later in 58.3% and 55.0% of patients, respectively. The mean FSS score at both time points was 4.1±1.7. 38 patients (15.7%) reported an increase in their perception of fatigue over the study period, 161 (66.5%) reported no change and 43 (17.8%) reported a decrease in their perception of fatigue. Of 6 baseline variables that were associated with the development of fatigue on bivariate analysis, (time since stroke, Motricity Index scores for the upper limb, 6MWT, MMSE, Stroke Impact Scale-Memory domain, and FSS score at baseline) only FSS score at time of discharge from hospital predicted an increase in FSS score (OR=0.50, 95% CI 0.38-0.64).
Lerdal et al. 2011 **Norway** **Retrospective study**	NA	115 patients ≥18 years, with first-ever stroke admitted to 2 hospitals who were cognitively competent. Mean age was 68.3 years.	Potential risk factors for fatigue were examined including: the presence of pre-stroke fatigue (identified if the patients reported fatigue of > 3-month	**Primary outcome:** Fatigue Severity Scale (FSS). Scores<4 indicated no fatigue, scores 4-4.9 indicated moderate fatigue and scores ≥5 indicated severe fatigue.	30% of patients reported pre-stroke fatigue. During the acute stage of stroke, 49 (43%) of patients were classified as experiencing no/low levels of fatigue, 38 (33%), moderate fatigue and 28 (24%) had severe fatigue.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			duration), sociodemographic factors, physical functioning (SF-36A, BI), sleep quality (Pittsburgh Sleep Quality Index), depressive symptoms (Beck Depression Inventory) and Body Mass Index.	Assessments were conducted within 15 days of hospitalization (mean: 4.6 days).	Independent predictors of acute, post-stroke fatigue were lower levels of physical functioning, depressive symptoms and pre-stroke fatigue.
Mead et al. 2011 **UK** **Prospective study**	NA	2, 253 patients included in the International Stroke study who had participated in the sub study evaluating quality of life after stroke. Mean age was 71.1 years.	Surviving patients were sent either the SF-36 or the EuroQOL by postal questionnaire an average of 64 weeks following randomization. Potential predictors of fatigue were examined, including: age, sex, stroke type (ischemic, hemorrhagic, indeterminate), location (total anterior circulation, partial anterior circulation syndrome, lacunar syndrome, posterior circulation syndrome), visible infarct, systolic blood pressure and atrial fibrillation.	**Primary outcome:** Fatigue, assessed using the vitality component of the SF-36.	1,080 patients completed the questionnaires. Of these, SF-36 vitality scores were recorded for 1,006 patients (93%). Median SF-36 vitality score was 37.5 (IQR 20, 55). 4 models to predict fatigue scores (as a continuous variable) were generated, based on the handling of missing data. All of them explained only a small amount of the variability, ranging from 0.4% to 5.4%. When missing values were excluded, younger age, male sex, ischemic stroke, POCS were associated with increasing SF-36 vitality scores. This model explained 3.7% of the variability in SF-36 vitality scores. When missing values were imputed using mean values, the same variables were associated with increasing fatigue scores. This model explained 3.4% of the variability.
Snaphaan et al. 2011 **Netherlands** **Retrospective study**	NA	108 patients, mean age of 65 years with acute, ischemic stroke admitted to a neurology department. Mean age was 65 years, 64% were male.	A model to predict post-stroke fatigue was developed using pre and post-stroke risk factors including: pre-stroke depression, the presence of white matter lesions (using the Age-Related White Matter Change Scale), cortical atrophy, stroke location, depression (Hospital Anxiety & Depression Scale), functional status (Barthel Index), handicap (mRS scale), global cognition (MMSE).	**Primary outcome:** Fatigue, assessed using the 8-question fatigue subscale of the Checklist Individual Strength, which evaluates symptoms of fatigue during the previous 2 weeks. Scores range from 8 to 56. A score > 35 indicates severe fatigue. Assessments were conducted at 2 (baseline) and 18 months (follow-up) post stroke.	The prevalence of fatigue was 35% at baseline and 33% at follow-up. 26% of patients reported fatigue at both assessment points, 9% reported fatigue at baseline, but not follow-up and 8% reported no fatigue at baseline, but did at follow-up. Independent risk factors for fatigue at baseline included younger age, symptoms of depression and anxiety and brainstem/cerebellar stroke. Independent risk factors for fatigue at 1.5 years included younger age, fatigue at baseline, and symptoms of anxiety and depression.

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Winward et al. 2009 **UK** **Retrospective study**	NA	73 participants with minor stroke and 76, with TIA who were participants in the Oxford Vascular study. Those who did not have recurrent stroke or major medical complication at 6 months, were functionally independent (Barthel Index score ≥18) and MMSE scores ≥24, were eligible.	Potential causes of fatigue were assessed, including: anxiety & depression, recent life events, obesity, thyroid function, and medications.	**Primary outcome:** Chalder Fatigue Scale (CFS), which consists of 11 short questions related to tiredness, energy, and the need to rest. Scores >3 indicate significant fatigue. Assessments were conducted at 6 months.	There were no baseline differences (assessed at time of stroke) between groups in demographics, vascular risk factors, anxiety/depression, medications, social or circumstances. There were no differences at 6 months between groups in BI scores, MMSE, or anxiety/depression scores. The median CFS score at 6 months was significantly higher for persons with stroke (4 vs. 1, p=0.0013). A higher proportion of persons with stroke reported significant fatigue (41, 56% vs. 22, 29%, p=0.008). A higher proportion of persons with stroke, who had initial NIHSS scores of 0 reported significant fatigue compared with TIAs with initial NIHSS scores of 0 (13, 57% vs. 22, 29%, p=0.015). Persons who felt they had not made a full recovery were more likely to be fatigued compared to those who felt they had (37/51 vs. 30/130, p<0.0001).
Christensen et al. 2008 **Denmark** **Controlled study**	NA	165 patients admitted to 3 acute stroke units following first-ever stroke. Median age was 64.5 years, 56% were men. 89% of patients had suffered a mild or moderate stroke. A reference group of 1,069 persons of similar ages was selected from the general population	Data on fatigue was collected by in-person interview, using all 5 dimensions from the Multidimensional Fatigue Inventory (MFI-20), including general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation (range of scores: 4-20, with higher scores indicating increasing fatigue). Additional data was collected from the medical chart. The incidence of fatigue was compared between persons with stroke and the reference group, over time. Assessments were conducted at baseline, 10 days, 3 months, 1 year and 2 years following stroke.	**Primary outcomes:** MFI-20 and pathological fatigue, defined as a general Fatigue score≥12.	Mean±sd MFI-20 scores for stroke patients at 10 days, 3 months, 1 and 3 years post stroke and the reference population were: General fatigue: 12±5, 11±5, 10±4, 10±4 vs. 10±4 Physical fatigue: 13±3, 12±3, 12±3, 12±3 vs. 9±4 Reduced activity: 13±5, 10±4, 10±4, 10±4 vs. 8±4 Reduced motivation: 8±3, 7±3, 7±3,7±3 vs. 7±3 Mental fatigue: 8±4, 8±4, 7±4,8±4 vs. 8±4 The mean differences in fatigue scores between stroke patients (3 months post-stroke) and the reference group, after adjusting for age, sex and living arrangements were: General Fatigue: 0.8, 95% CI: 0.0, 1.6, p = 0.04 Physical Fatigue: 2.1, 95% CI: 1.3, 2.8, p<0.0001 Reduced Activity: 1.2, 95% CI: 0.5, 1.9, p = 0.001), Reduced Motivation: –0.2, 95% CI: –0.7, 0.4, p = 0.57), Mental Fatigue: –0.2, 95% CI: –0.8, 0.5, p = 0.60. Among stroke patients, fatigue scores declined significantly and remained stable for the remainder of follow-up. Pathological fatigue was present at 10 days, 3 months,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					6 months, 1 year and 2 years in 59%, 44% and 38% and 40% of stroke patients, respectively. Low Barthel Index scores were independently associated with fatigue (MFI-20) scores across scale dimensions and time.
Van de Port et al. 2007 **Netherlands** **Retrospective study**	NA	223 patients, > 18 years, admitted for inpatient rehabilitation following unilateral, first-ever, supratentorial stroke, pre-morbid Barthel Index score≥18. Mean age was 57 years, 60% were male.	The impact of fatigue on ADL, measured by the Barthel Index (0-20), IADL, measured by the Frenchay Activities Index (0-45) and HRQoL, measured by the Sickness Impact Scale (0-100%), was explored, by in-person interviews at 6, 12 and 36 months following stroke.	**Primary outcome:** Fatigue, identified by scores of ≥4 on the Severity Scale.	At 3, 6 and 36 months, mean FSS scores were: 4.5, 4.7 and 4.3, respectively. The percentage of patients considered fatigued at 6, 12 and 36 months were: 68%, 74% and 58%, respectively. Fatigue was not associated with performance on ADL, but was associated with IADL and HRQoL. After controlling for depression and motor impairment, there was no longer a significant relationship between fatigue and IADL. The relationship between fatigue and HRQoL remained significant after adjusting for depression.
Schepers et al. 2006 **Netherlands** **Retrospective study**	NA	167 patients >18 years, consecutively admitted to one of 4 rehabilitation centres with first-ever unilateral, supratentorial lesion. Mean age was 56.4 years, 59% were male.	Post stroke impairments were assessed at 6 months and 1-year following stroke. A model to predict the development of PSF was developed using factors that were significantly related on univariate analyses, including scores on the Multidimensional Health Locus of Control (MHLC) scale, Motricity Index (MI), MMSE, Trail-Making Test part b (TMT-B), Centre of Epidemiological Studies Depression Scale (CES-D), with a score of >16 indicating depression.	**Primary outcome:** Fatigue, identified by a score of ≥4 using the Fatigue Severity Scale (FSS)	Fatigue was present at baseline, 6 months and 1 year in 51.5%, 64.1% and 69.5% of patients, respectively. Fatigue was present in 37.7% of patients, and absent in 17.4%, at all assessment points. Of the patients reporting fatigue at 1 year, 29.3% were also depressed. Independent predictors of fatigue at 1 year included increasing age, female sex, CES-D scores, MHLC (powerful others subscale).
Choi-Kwon et al. 2005 **South Korea** **Retrospective study**	NA	220 consecutively admitted outpatients, aged 40-80 years, recruited an average of 15 months following first-ever stroke. Mean age was 60 years. Persons with stroke onset<3	Factors related to the development of PSF were evaluated: motor impairment, demographics, SES, current medications, imaging, post-stroke depression (PSD) (indicated	**Primary outcome:** Fatigue, assessed using the 10- point VAS, the 9-item Fatigue Severity Scale (FSS)	125 patients (57%) had PSF, 53 (24%) had PSD, 38 (17%) had emotional incontinence and 83 (38%) had pre-stroke fatigue. Factors related to PSF included: being unemployed, loss or change of the job after stroke, smoking, high mRS score, the presence of any residual neurological

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		months, mRS score ≥4, severe, pre-stroke depression, MMSE score ≤23, and lack of relatives to confirm +/- post-stroke fatigue (PSF), were excluded.	by Geriatric Depression Scale scores >10) and emotional incontinence (identified by relatives if patients showed excessive or inappropriate laughing, crying or both as compared to the premorbid state), pre-stroke fatigue.		deficits, dysarthria, pre-stroke fatigue, insomnia, PSD, inappropriate/excessive laughing and a decrease in appetite or sexual activities. The following factors were independently related to PSF: pre-stroke fatigue (OR= 33.46, 95% CI 12.25 to 91.36, p<0.01, high mRS score (OR= 3.25, 95% CI 1.29 to 8.18, p<0.050), PSD (OR=2.67, 95% CI 1.04 to 6.85, p<0.05), decreased sexual activity (OR=2.46, 95% CI 1.07 to 5.66, p<0.05).
Glader et al. 2002 **Sweden** **Prospective study**	NA	5,189 patients who were alive 2 years following stroke, included in the Riks-Stroke national stroke registry.	Patients were surveyed by mail questionnaire 2 years following stroke, to determine their ability to perform ADLs, their current living situation and to determine whether fatigue was an independent risk factor for mortality.	**Primary outcome:** Fatigue was assessed by asking the question, “do you feel tired?” Possible response categories were never, sometimes, often or always. Questions related to ADL performance, self-reported depression, anxiety and pain were also included.	Survey response was 79% (n=4,023). 366 (10%) of respondents reported always being tired, while 1,070 (29.2%) reported often being tired. Patients who reported always being tired were older, on average (74.5 vs. 71.5 years, p<0.001), single prior to stroke, lived in an institution prior to stroke, dependent for ADL prior to stroke and had experienced a recurrent stroke.

Treatment for Post-Stroke Fatigue

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Wu et al. 2015 **UK** **Cochrane Review**	NA	Results from 12 RCTs (n=1,254) including adult participants with and without post stroke fatigue (PSF). Mean time since stroke varied from 4 days to 7 years.	Treatments included: interventions to treat PSF (pharmacological n=4, non-pharmacological n=4). There were no trials designed to prevent PSF. In 4 trials, PSF was not the primary target of investigation, but fatigue was reported as an outcome. Interventions in these trials included CPAP, a chronic-disease self-management program (delayed vs. immediate participation, tirilazad mesylate and antidepressants.	**Primary outcome:** Fatigue at end of study	**Trials designed to treat fatigue** Using the results from 7 trials (5 pharmacological, 2 no-pharmacological), treatment was associated with a significant reduction in fatigue scores (WMD= -1.07, 95% CI -1.93, -0.21, p=0.014). **Trials not designed to treat fatigue** No pooled analyses were conducted. No intervention was associated with a significant reduction in PSF scores after treatment.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Non-pharmacological Treatments					
Zedlitz et al. 2013 **Netherlands** **RCT**	CA: ☑ Blinding patient: ☒ assessor: ☑ ITT: ☑	83 community dwelling individuals who were independent in ambulation, recruited from rehabilitation centres, aged 18-70 years with severe fatigue >4 months post stroke. Mean age was 55 years, 53% were male. Mean time since stroke onset was 3.9 years.	Participants were randomized to receive 12-weeks of group cognitive treatment (CO; n=45) or group cognitive treatment combined with graded activity training (COGRAT; n=38). Cognitive treatment consisted of cognitive behavioural therapy and compensatory strategy teaching. Those in the COGRAT condition additionally received 24, 2-hour sessions of graded activity training, which consisted of treadmill walking, strength training, and homework assignments.	**Primary outcomes:** The Checklist Individual Strength-fatigue subscale (CIS-f) and the Fatigue Self-Observation List (SOL-f) **Secondary outcomes:** The Hospital Anxiety and Depression Scale, the Stroek-Adapted Sickness Impact Profile 30, and the 6-Minute Walk Test **Timing of assessment:** Baseline, at the end of treatment, and at 6-month follow-up.	Participants who received COGRAT were significantly more likely to experience clinically relevant improvement in fatigue severity (a decrease in CIS-f score of ≥8 points), compared to those in the CO group (57.9% vs. 24.4%, p=0.002). Lost to follow-up**:** COGRAT=13.2%, CO=22.2%
Clarke et al. 2012 **New Zealand** **RCT**	CA: ☒ Blinding patient: ☒ assessor: ☒ ITT: ☒	19 patients with fatigue ≤18 months post stroke. Patients were excluded if they had significant impairments or were medically unstable. Mean age was 72 years, 62% were male. Mean time since stroke onset was 8 months.	Participants were randomized to receive fatigue management (n=10) or general stroke education (n=10). Participants in both conditions received a total of 6, 60-minute group psychoeducation sessions.	**Primary outcome**: Fatigue Severity Scale (FSS). **Secondary outcomes**: Visual analogue scale for fatigue, Checklist of Individual Strength, Short Form-36, Hospital Anxiety and Depression Scale, modified Rankin Scale, and the Barthel Index.	Mean scores on the Fatigue Severity Scale decreased significantly from baseline to post-intervention for participants in both groups (p=0.02). These changes were maintained at the 3-month follow-up. No significant between group differences were reported for any of the outcomes the end of the intervention.
Johansson et al. 2012 **Sweden** **RCT**	CA: ☒ Blinding patient: ☒ assessor: ☒ ITT: ☒	29 patients, 18 with stroke and 11 with TBI, with mental fatigue, aged 30-65 years, who were within 12 months of stroke or TIA, with Mental Fatigue Scale (MFS) ≥ 10	Participants were randomized to receive a Mindfulness –Based Stress Reduction (MBSR; n=15) program or to a wait list control group (n=14). The MBSR program included Hatha yoga, body scan, and sitting meditation and consisted of 8 weekly group sessions (2.5 hour per session), a full-day retreat, and 45 minutes of home practice 6 days/week.	**Primary outcome**: Mental Fatigue Scale (MFS). **Secondary outcomes**: The Comprehensive Psychopathological Rating Scale, the WAIS-III digit symbol-coding and digit span subscales, and the Trail Making Test.	At the end of study, participants who received the MBSR program reported a significantly greater decrease in MFS scores (p<0.01). The treatment group also reported a significant decrease in depression (p<0.01) and anxiety (P<0.01), although between group comparisons were not significant. Following the waitlist period, participants from the control group received the MBSR program and also reported a significant decline in MFS scores (p<0.01). Lost to follow-up: 20% in the active treatment group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Brown et al. 2011 **USA** **RCT** ***Sleep Apnea Treatment after Stroke (SATS)***	CA: ☒ Blinding patient: ☑ assessor: ☑ ITT: n/a	54 patients admitted to a Neurology services with acute ischemic stroke of ≤7 days duration, with a mRS score >1 and who tested positive for sleep apnea.	32 patients were randomized to receive active (n=15) or sham (n=17) continuous positive airway pressure (CPAP) for 3 months.	**Primary outcomes:** Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), an 8-item scale with each item scored from 0 to 3. Scores range from 0-24 with higher scores indicating increasing sleepiness. Scores ≥9 indicate a problem with sleepiness that should prompt medical attention, PHQ-9, Barthel Index (BI).	At 3 months, the median (IQR) scores for patients in the active and sham groups were: FSS: 2.6 (2.0, 4.1) vs. 2.4 (1.4, 3.0) ESS: 8 (6,9) vs. 7 (4,10) PHQ-9: 5 (4,6) vs. 2 (2,3) BI: 95 (90,100) vs. 100 (95, 100) (no inferential statistics are reported as the trial was designed as a feasibility study) Lost to follow-up: active CPAP, n=7, sham CPAP, n=6.
Lorig et al. 2001 **USA** **RCT**	CA: ☒ Blinding patient: ☒ assessor: ☑ ITT: ☒	1,140 participants (125 with stroke) > 40 years living with heart or lung disease, stroke, or arthritis who were recruited from the community. Average age was 65 years.	831 subjects were randomized to participate in a 6-month chronic disease self-management program (CDSMP) immediately after randomization, or after a 6-month delay. The program was led by 2 peer leaders and was provided over 7 weeks, 2.5 hours weekly. Content included: exercise programs, cognitive symptom management techniques, such as guided relaxation and distraction, nutritional change, fatigue and sleep management, use of community resources, communication with health professionals and others and health-related problem-solving and decision making.	**Primary outcomes:** Number of ER/MD visits, self-rated health scale (scored from 1-5, with lower scores indicating better health), disability, (scored from 0-3 using a modified version of the Health Assessment Questionnaire disability scale, with lower scored indicating less disability), energy/fatigue (scored from 0-5 with higher scores indicated less fatigue, using the long-form Medical Outcomes Scale subscale), self-efficacy (scored from 1-10 with higher scores indicating better performance). Assessments were conducted at baseline, after the intervention and at 1 and 2 years. Data were collected by mailed questionnaires.	Data were available for 683 subjects at 1 year and 533 at 2 years. Data from the 2 groups were combined. Mean ±sd fatigue scores at baseline, 1 year and 2 years were: 2.20±1.08, 2.24±1.10 and 2.28±1.09. Mean ± sd fatigue score changes from baseline at 1 and 2 years were: 0.045±0.85, p=0.165 and 0.077±0.912, p=0.054. There was significant improvement from baseline to 1 year in the number of ER/MD visits, disability, health distress, and self-efficacy. There were significant improvements from baseline to 2 years in the number of ER/MD visits, health distress, and self-efficacy.
Pharmacological Treatments					
Bivard et al. 2017 **Australia** **Phase II RCT** ***Modafinil in Debilitating Fatigue After Stroke (MIDAS)***	CA: ☑ Blinding patient: ☑ assessor: ☑ ITT: ☑	36 patients >18 years of age with a history of stroke ≥ 3 months previously and a score of ≥60 across all domains of the Multidimensional Fatigue Inventory (MFI)-20. Mean age was 63 years, 61% were male. Mean time post stroke was 9 months. Mean baseline MFI score was 72.	Participants were randomized to receive 200 mg modafinil or placebo, daily for 6 weeks. After a 1- week washout period, participants crossed over and received the other treatment for a second 6-week period.	**Primary outcome:** MFI-20 **Secondary outcomes:** Montreal Cognitive Assessment (MoCA), Fatigue Severity Scale (FSS), the Depression, Anxiety, and Stress Scale (DASS), and the Stroke-	Treatment with modafinil was associated with a significantly greater decrease in mean total MFI-20 scores (MD= −7.38, 95% CI −21.76 to −2.99; *P*<0.001), mean FSS scores (MD= -6.31, 95% CI -10.7 to -1.9, p=0.048) and a significantly greater increase in total mean SSQoL scores (MD=11.8, 95% CI 2.3 to 21.3, p=0.015). There was no significant improvement in MoCA or DASS scores associated with modafinil.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Specific Quality of Life (SSQoL) scale Assessments were conducted at baseline, 6 weeks, 7 weeks (1-week after wash-out period) and at the end of the second 6-week treatment period.	There were 12 adverse events (modafinil=5, placebo=7), but no serious adverse events.
Poulsen et al. 2015 **Denmark** **RCT**	CA: ☑ Blinding patient: ☑ assessor: ☑ ITT: ☒	41 patients ≥18 years who had suffered a stroke within the previous 14 days, with a premorbid mRS score of ≤3, and with poststroke fatigue (Multidimensional Fatigue Inventory-20 General Fatigue Domain [MFI-20 GF] score of ≥12). Mean age was 70 years, 54% were women.	Patients were randomized 1:1 to receive 400-mg modafinil or placebo for 90 days	**Primary outcome:** MFI-20 **Secondary outcome:** FSS, FSS-7, BI Assessments were conducted at baseline, 30,90 and 180 days	At 90 days, there was no significant difference between groups in the median MFI-20 GF score (11 modafinil vs placebo 14, p=0.32). There were no differences between groups in the median score of other MFI domains (physical fatigue, reduced activity, reduced motivation). Median FSS and FSS-7 were significantly lower at 90 days for patients in the modafinil group (36 vs. 49.5, p=0.02 and 22 vs. 37.5, p=0.042). There were no serious adverse events. There were 5 losses to follow-up
Karaiskos et al. 2012 **Greece** **RCT**	CA: ☒ Blinding patient: ☒ assessor: ☒ ITT: ☒	60 patients diagnosed with post-stroke depression following a first-ever stroke that had occurred within 12-months of study recruitment. Mean age was 53 years.	Participants were randomized to receive duloxetine (titrated from 30 to 60-120 mg/day; n=20), citalopram (20-40 mg/day; n=20), or sertraline (50-200 mg/day; n=20) for 3 months.	**Primary outcomes:** Fatigue Severity Score (FSS). **Secondary outcomes:** Mini-Mental State Exam, the modified Rankin Scale, and the Hamilton Rating Scale for Depression and Anxiety. Assessments were conducted at baseline, and at 1, 2, and 3 months following treatment initiation.	Treatment with pharmacotherapy was not associated with significant improvement in fatigue severity at any time. Mean FSS scores from baseline to study end: Duloxetine: 4.5 (1.4) to 3.7 (1.1) Citalopram: 4.5 (1.5) to 3.9 (1.3) Sertraline: 4.6 (1.6) to 4.0 (1.4)
Choi-Kwon et al. 2007 **South Korea** **RCT**	CA: ☒ Blinding patient: ☑ assessor: ☑ ITT: ☑	112 consecutive patients attending an outpatient clinic, an average of 14.5 months following reporting symptoms of post-stroke fatigue (PSF). Average age was 57 years. Patients with SAH or TIA, MMSE score ≤23, severe communication difficulties, and those with a history of pre-stroke depression, were	83 patients were randomized to receive 20 mg/day of fluoxetine (n=40) or placebo, (n=43) for 3 months.	**Primary outcomes:** Fatigue (10- point VAS), Fatigue Severity Scale (9-items, each scored on a 7-point Likert Scale, with higher scores indicating more severe fatigue). **Secondary outcomes:** +/- of: depression, (based on Beck Depression Inventory score>13) post-stroke	At baseline, the number of patients in the fluoxetine and control groups with depression, excessive laughing, crying and anger were: 12 vs. 20, p=ns, 29 vs. 30, p=ns, 9 vs. 7, p=ns, and 26 vs. 30, p=ns There were no significant differences in the number of patients with PSF at 3 or 6 months. At 6 months, 34 patients (85%) in the fluoxetine group reported PSF compared with 40 (93%) in the control group. The percentage change in mean (±sd) VAS scores at 6

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		excluded.		emotional incontinence (patient/relative reporting 2+ episodes of inappropriate laughing or crying), post-stroke anger proneness (post stroke Spielberger Trait Anger Scale score >pre-stroke score). Assessments were conducted at baseline, 3 and 6 months.	months for patients in the fluoxetine and control groups were: -11.9±40.0 vs. -8.1±31.0, p=ns The percentage change in mean (±sd) FSS scores at 6 months for patients in the fluoxetine and control groups were: -9.8±28.8 vs. -9.2±24.4, p=ns. Fewer patients in the fluoxetine group had depression at 6 months (n=5, 12.5% vs. n=13, 30.2%, p=0.05). At 3 months, fewer patients in the fluoxetine group reported excessive/inappropriate crying (n=16, 40% vs. n=27, 62.8%, p=0.038). Adverse events: No reporting.

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