HEART & STROKE FOUNDATION | CANADIAN Stroke BEST PRACTICE RECOMMENDATIONS

# CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

## Mood, Cognition and Fatigue Following Stroke

## Evidence Tables

## *Post-Stroke Fatigue*

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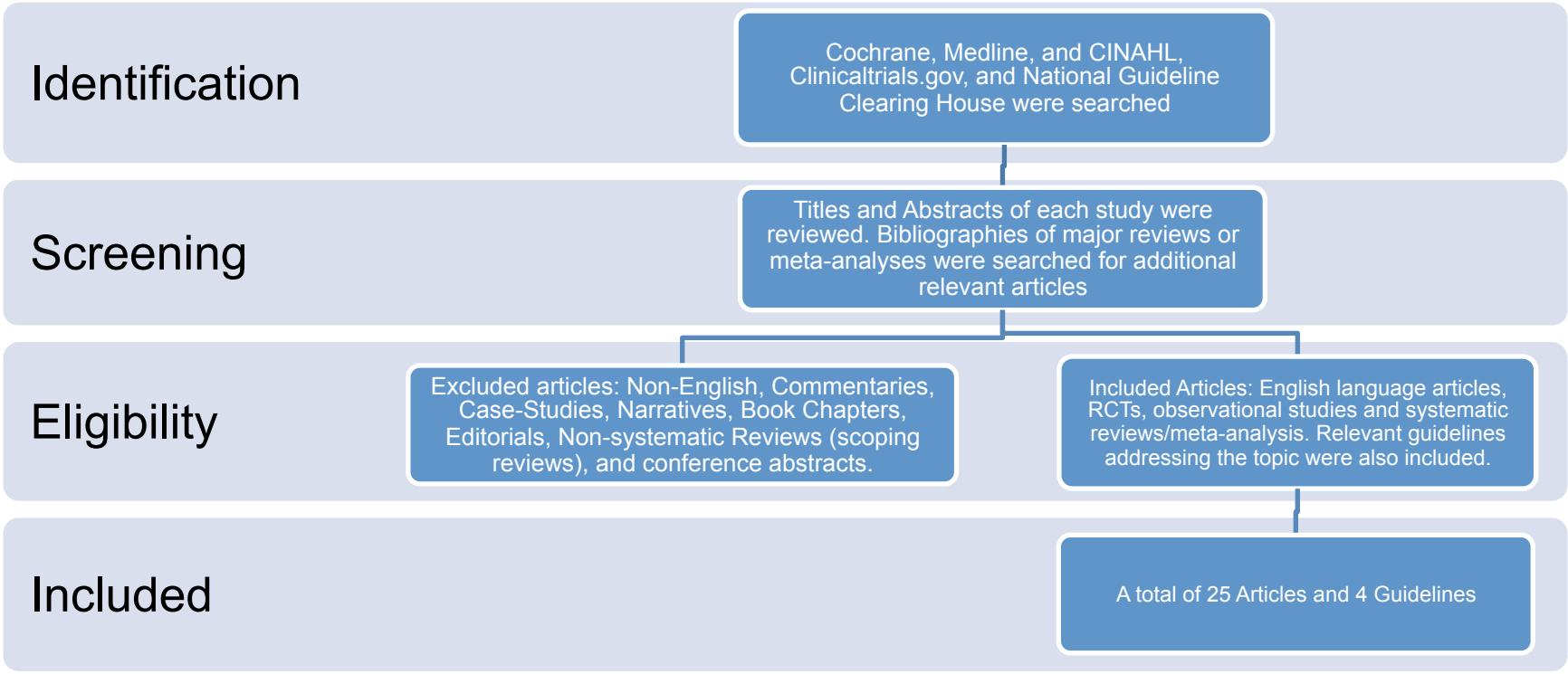
# Search Strategy




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 25 articles and 4 guidelines were included.

# Published Guidelines

| Guideline | Recommendations |
|---|---|
| **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<br><br>Patients with post-stroke fatigue should be screened for depression<br><br>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 |
| **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)**<br><br>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)** |
| **Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, Katz RC, Lamberty K, Reker D. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke, 2005;36:e100-e143.** | None |

# 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 |
|---|---|---|---|---|---|
| **Duncan et al. 2012**<br><br>**UK**<br><br>**Systematic Review** | NA | 9 observational studies (n=959) assessing fatigue in stroke patients at two or more time points. Retrospective studies, those recruiting participants >6 months post stroke, and those using unstructured assessments of fatigue were excluded. | Articles were identified through a combination of electronic and manual search strategies. | Frequency of fatigue. | The frequency of fatigue was reported to range from 35% to 92% across the included studies. 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**<br><br>**Germany**<br><br>**Observational** | NA | 541 patients with acute ischemic stroke admitted to hospital (patients were included in the Bergen Stroke Study). Average age was 67.7 years. | Surviving patients received a postal questionnaire >6 months following stroke. | Pain (10-point VAS), fatigue (Fatigue Severity Scale) and depression (Hospital Anxiety & Depression Scale, depression component).<br><br>FSS score ≥5 indicated fatigue. | 328 patients completed the questionnaire, an average 372 days following stroke.<br><br>141 (46%) patients reported fatigue.<br>The mean±sd FSS score was 4.4±1.8<br>157 (48%) patients reported pain (VAS score>0)<br>61 (19% ) patients reported being depressed<br><br>Pain and depression were correlated with fatigue scores. |
| **Parks et al. 2012**<br><br>**Canada**<br><br>**Observational** | NA | 228 individuals' 12-months following an ischemic stroke.<br><br>**Exclusion criteria:**<br>TIA, subarachnoid hemorrhage, subdural hematoma, cerebral hemorrhage, decreased levels of consciousness, dysphasia or severe cognitive impairment.<br><br>43.7% of those included in the original study cohort participated in the one-year follow-up. | Trained stroke assessors conducted interviews with participants to evaluate function, quality of life, depression, and fatigue. | Presence and severity of post stroke fatigue was assessed with the Fatigue Impact Scale (FIS). Additional assessments included the Barthel Index, the modified Rankin Score, the Reintegration into Normal Living scale, and the Geriatric Depression Scale. | 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.<br><br>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 ($p<0.05$). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Van Eijsden et al. 2012**<br><br>**Netherlands**<br><br>**Observational study** | NA | 250 patients were recruited at the time of hospital discharge from inpatient rehabilitation.<br><br>Inclusion criteria: ≥18 years, ability to walk at least 10 metres without assistance, discharge destination was home, cognitively intact and ability to communicate. Average age was 57.1 years. | 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). | Fatigue was assessed using the Fatigue Severity Scale (FSS).<br><br>Patients with a total score of ≥4 points were classified as "fatigued."<br><br>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.<br><br>Fatigue was reported at baseline and 24 weeks later in 58.3% and 55.0% of patients, respectively.<br><br>The mean FSS score at both time points was 4.1±1.7.<br><br>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.<br><br>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**<br><br>**Norway**<br><br>**Observational study** | NA | 115 patients ≥18 years, with first-ever stroke admitted to 2 hospitals who were cognitively competent. Average 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 duration), sociodemographic factors, physical functioning (SF-36A, BI), sleep quality (Pittsburgh Sleep Quality Index), depressive symptoms (Beck Depression Inventory) and Body Mass Index. | Fatigue was assessed by the Fatigue Severity Scale (FSS). Scores<4 indicated no fatigue, scores 4-4.9 indicated moderate fatigue and scores≥5 indicated severe fatigue.<br><br>Assessments were conducted within 15 days of hospitalization (average: 4.6 days). | 30% of patients reported pre-stroke fatigue.<br><br>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.<br><br>Independent predictors of acute, post-stroke fatigue were lower levels of physical functioning, depressive symptoms and pre-stroke fatigue. |
| **Mead et al. 2011** | NA | 2, 253 patients included in | Surviving patients were | Fatigue was assessed | 1,080 patients completed the questionnaires. Of |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **UK**<br><br>**Observational study** | | the International Stroke study who had participated in the sub study evaluating quality of life after stroke. Average age was 71.1 years. | sent either the SF-36 or the EuroQOL by postal questionnaire an average of 64 weeks following randomization.<br><br>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. | using the vitality component of the SF-36. | these, SF-36 vitality scores were recorded for 1,006 patients (93%).<br><br>Median SF-36 vitality score was 37.5 (IQR 20, 55).<br><br>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%.<br><br>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.<br><br>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**<br><br>**Netherlands**<br><br>**Observational study** | NA | 108 patients, mean age of 65 years with acute, ischemic stroke admitted to a neurology department. | 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). | The presence of fatigue was 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.<br><br>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.<br><br>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.<br><br>Independent risk factors for fatigue at baseline included younger age, symptoms of depression and anxiety and brainstem/cerebellar stroke.<br><br>Independent risk factors for fatigue at 1.5 years included younger age, fatigue at baseline, and symptoms of anxiety and depression. |
| **Naess et al. 2010** | NA | 824 patients admitted to hospital following acute | Surviving patients were survey by postal | Post-stroke fatigue was assessed using the Fatigue | 408 patients returned the questionnaire. 124 patients had died. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Germany**<br><br>**Observational study** | | ischemic or hemorrhagic stroke, included in the Bergen Stroke Study. Average age was 68.1 years. | questionnaire ≥ 6 months post stroke to determine the incidence of post-stroke pain (10-point VAS), and headache. Risk factors included fatigue, anxiety/depression, co-morbid medical conditions, stroke severity, dependency, sleep disturbances. | Severity Scale (FSS).<br><br>Scores ≥5 indicated the presence of fatigue. | Post-stroke pain was reported by 182 (44.6%) patients.<br><br>The mean FFS scores were higher for patients reporting pain compared to those without pain (5.0 vs. 3.7, p<0.001). Fatigue was an independent predictor of pain (OR=3.1,p<0.001).<br><br>The mean FFS scores were higher for patients reporting headache (5.4 vs. 4.1, p<0.001). Fatigue was an independent predictor of headache (OR=3.4, p=0.001). |
| **Winward et al. 2009**<br><br>**UK**<br><br>**Observational study** | NA | 73 subjects with minor stroke and 76 subjects with TIA who were participants in the Oxford Vascular study. Subjects 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. | Chalder Fatigue Scale (CFS), which consists of 11 short questions related to tiredness, energy, and the need to rest. Scores >3 indicate significant fatigue.<br><br>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.<br><br>There were no differences at 6 months between groups in BI scores, MMSE, or anxiety/depression scores.<br><br>The median CFS score at 6 months was higher for subjects with stroke (4 vs. 1, p=0.0013).<br><br>A higher proportion of subjects with stroke reported significant fatigue (41, 56% vs. 22, 29%, p=0.008).<br><br>A higher proportion of subjects with stroke, who had initial NIHSS scores of 0 reported significant reported significant fatigue compared with TIAs with initial NIHSS scores of 0 (13, 57% vs. 22, 29%, p=0.015).<br><br>Subjects 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** | NA | 165 out of 717 consecutive patients recruited from 3 acute stroke units with acute | Data on sociodemographic and clinical characteristics of | Multidimensional Fatigue Inventory (MFI-20), a 5-dimnsion scale including | Mean±sd MFI-20 scores for stroke patients at 10 days, 3 months, 1 and 3 years post stroke and the reference population were: |

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|---|---|---|---|---|---|
| **Denmark**<br><br>**Controlled study** | | stroke who were eligible.<br><br>Exclusion criteria: previous stroke, dementia, or major neurologic condition, psychiatric disease (depression, drug/alcohol abuse), deteriorating health due to comorbid condition, discharge from hospital within 9 days of admission.<br><br>A reference group of 1,069 person of similar ages was selected from the general population | the stroke patients were collected in-person or by review of medical records. Clinical variables included lesion location and Scandinavian Stroke Scale (SSS) score<br>Barthel Index (BI), new-onset depression (assessed using the Major Depression Inventory), use of antidepressants, and Charlson Comorbidity Index (defined by three levels of comorbidity for each patient: none, low, high) were collected and compared between groups. | general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation (range of scores: 4-20, with higher scores indicating increasing fatigue). Pathological fatigue, defined as a general Fatigue score≥12.<br><br>Assessments were conducted at baseline, 10 days, 3 months, 1 year and 2 years following stroke. | General fatigue: 12±5, 11±5, 10±4, 10±4 vs. 10±4<br>Physical fatigue: 13±3, 12±3, 12±3, 12±3 vs. 9±4<br>Reduced activity: 13±5, 10±4, 10±4, 10±4 vs. 8±4<br>Reduced motivation: 8±3, 7±3, 7±3,7±3 vs. 7±3<br>Mental fatigue: 8±4, 8±4, 7±4,8±4 vs. 8±4<br><br>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:<br>General Fatigue: 0.8, 95% CI: 0.0, 1.6, p = 0.04<br>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),<br>Mental Fatigue: –0.2, 95% CI: –0.8, 0.5, p = 0.60.<br><br>Among stroke patients, fatigue scores declined significantly and remained stable for the remainder of follow-up.<br><br>Pathological fatigue was present at 10 days, 3 months, 6 months, 1 year and 2 years in 59%, 44% and 38% and 40% of patients, respectively.<br><br>Low BI scores were independently associated with fatigue (MFI-20) scores across scale dimensions and time. |
| **Van de Port et al. 2007**<br><br>**Netherlands**<br><br>**Observational study** | NA | 223 acute stroke patients admitted for inpatient rehabilitation at 4 centres.<br><br>Inclusion criteria: > 18 years, unilateral, first-ever, supratentorial stroke, pre-morbid Barthel Index score≥18. | 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. | Fatigue was assessed using the Fatigue Severity Scale. Scores ≥4 indicated fatigue.<br><br>Assessments were conducted, by in-person interviews at 6, 12 and 36 months following stroke. | At 3, 6 and 36 months, mean FSS scores were: 4.5, 4.7 and 4.3, respectively.<br><br>The percentage of patients considered fatigued at 6, 12 and 36 months were: 68%, 74% and 58%, respectively.<br><br>Fatigue was not associated with performance on ADL, but was associated with IADL and HRQoL.<br><br>After controlling for depression and motor |

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| | | | | | impairment, there was no longer a significant relationship between fatigue and IADL.<br><br>The relationship between fatigue and HRQoL remained significant after adjusting for depression. |
| **Schepers et al. 2006**<br><br>**Netherlands**<br><br>**Observational study** | NA | 167 patients >18 years, consecutively admitted to one of 4 rehabilitation centres with first-ever unilateral, supratentorial lesion. Average age was 56.4 years. | Post stroke impairments were assessed at 6 months and 1-year following stroke.<br><br>A model to predict the development of PSF was developed using factors that were significantly related on univariate analyses. | Evaluations included assessments of fatigue, using the Fatigue Severity Scale (FSS), whereby a score of 4 or more indicated the presence of fatigue, the Multidimensional Health Locus of Control (MHLC) scale (3 subscales, each having 6 items and scored on a 6-point scale), Motricity Index (MI), MMSE, Trail-Making Test part b (TMT-B), Centre of Epidemiological Studies Depression Scale (CES-D), a 20-item, self-report questionnaire, with a score of >16 indicating depression. | Fatigue was present at baseline, 6 months and 1 year in 51.5%, 64.1% and 69.5% of patients, respectively.<br><br>Fatigue was present in 37.7% of patients, and absent in 17.4%, at all assessment points.<br><br>Of the patients reporting fatigue at 1 year, 29.3% were also depressed.<br><br>Independent predictors of fatigue at 1 year included increasing age, female sex, CES-D scores, MHLC (powerful others subscale). |
| **Choi-Kwan et al. 2005**<br><br>**South Korea**<br><br>**Observational study** | NA | 220 consecutive outpatients, mean age of 60 years, an average of 15 months post stroke.<br><br>Exclusions included: stroke onset<3 months, mRS score ≥4, ages <40 and > 80 years, previous stroke, multiple or bilateral lesions, severe, pre-stroke depression, MMSE score ≤23, absence of relatives to confirm +/- post-stroke | Factors related to the development of PSF were evaluated: motor impairment, demographics, SES, current medications, imaging (CT or MRI), post-stroke depression (PSD) (indicated by Geriatric Depression Scale scores >10) and emotional incontinence (identified by relatives if patients showed | Fatigue was assessed using the 10- point VAS, Fatigue Severity Scale (FSS), a 9-item scale, each scored on a 7-point Likert Scale, with higher scores indicating more severe fatigue.<br><br>A model to predict the development of PSF was developed using factors that were significantly related, on univariate | 157 patients (57%) had PSF, 53 (24%) had PSD, 38 (17%) had emotional incontinence and 83 (38%) had pre-stroke fatigue.<br><br>Factors related to PSF included: being unemployed,<br>loss or change of the job after stroke, smoking, high mRS score, the presence of any residual neurological deficits, dysarthria, pre-stroke fatigue, insomnia, PSD, inappropriate/excessive laughing and a decrease in appetite or sexual activities.<br><br>The following factors were independently related |

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| | | fatigue (PSF). | excessive or inappropriate laughing, crying or both as compared to the premorbid state), pre-stroke fatigue. | analyses. | to PSF: pre-stroke fatigue (OR= 33.46, 95% CI 12.25 to 91.36, p<0.01, 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). |
| **Carlsson et al. 2003**<br><br>**Sweden**<br><br>**Observational study** | NA | 82 patients <75 years, admitted to a stroke unit with first-ever, mild stroke (BI scores 50-100, assessed during the first week of admission) who lived with a spouse prior to stroke. | The prevalence of fatigue, lack of ability to concentrate, memory disturbances, changes in emotional stability, stress resistance, anxiety and uneasiness were explored. | Perceived symptoms of fatigue were evaluated by interview.<br><br>Assessments were conducted at one year post stroke. | At 1 year, 5 patients had died and 2 patients dropped out.<br><br>The number (%) of patients with the following symptoms was:<br>Fatigue: 54 (72%)<br>Memory dysfunction: 41 (55%)<br>Concentration difficulties: 36 (48%)<br>Irritability: 31 (42%) |
| **De Groot et al. 2003**<br><br>**Canada**<br><br>**Review** | n/a | 1000 articles were identified that examined fatigue in stroke or other neurological disorders. | Articles were identified through a combination of electronic and manual search strategies. | Frequency, duration severity, and treatment options were considered. | The reported frequency of post stroke fatigue was found to range from 30% to 68%. Although some studies have reported significant associations between post stroke fatigue and demographic variables (including older age and female sex), such findings have not been consistent. Treatment of fatigue has been investigated in other patient populations but further research is needed to identify interventions that are beneficial post-stroke. |
| **Glader et al. 2002**<br><br>**Sweden**<br><br>**Observational 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. | Fatigue was assessed by asking the question, “do you feel tired?” Possible response categories were never, sometimes, often or always.<br><br>Questions related to ADL performance, self-reported depression, anxiety and pain were also included. | Survey response was 79% (n=4,023).<br><br>366 (10%) of respondents reported always being tired, while 1,070 (29.2%) reported often being tired.<br><br>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.<br><br>At 3 years following stroke, increasing age, (OR=1.06, 95% CI 1.04 to 1.307, p<0.001), male sex (OR=1.46, 95% CI 1.14 to 1.86, p=0.002), ICH (OR=1.64, 95% CI 1.02 to 5.30, p=0.04), |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | dependence in ADL at 2 years (OR=2.65, 95% CI 1.96 to 3.59, p<0.001), speech impairment (OR=1.40, 95% CI 1.10 to 1.80, p=0.007), fatigue (OR (often)=1.31, 95% CI 1.01 to 1.71, p=0.045, OR (always)=1.85, 95% CI 1.35 to 2.54, p<0.001) were independent predictors of mortality. |
| **Ingles et al. 1999**<br><br>**Canada**<br><br>**Controlled study** | NA | 88 out of 181 patients who had been admitted consecutively to a hospital stroke service, who met study criteria were included. Average age was 66 years).<br><br>Inclusion criteria: Ischemic stroke or ICH, discharged to their homes or to a rehabilitation centre.<br><br>Exclusion criteria: recurrent stroke following initial admission, other neurological disease, non-English speaker, severe communication difficulties.<br><br>An additional 56 volunteers, recruited from a seniors apartment complex were also recruited. | Postal questionnaire, enquiring about health and lifestyle were to be completed by patients, with help from caregivers, if required. Stroke related measures were available from a stroke registry.<br><br>Respondents were also interviewed by telephone.<br><br>Comparisons were made between stroke and non-stroke participants. | Fatigue Impact Scale (FIS), a 40-item scale (3 domains), with a maximum score=160.<br><br>Geriatric Depression Scale (GDS). | The number of participants reporting problems with fatigue was higher in the stroke group (68% vs. 36%, p<0.001).<br><br>The mean ±sd FIS scores for each of the domains for stroke patients and controls were:<br>Cognitive: 27.5±27.1 vs. 18.3±20.1<br>Physical: 43.1±24.7 vs. 27.8±18.9, p<0.02<br>Psychosocial: 33.5±24.4 vs. 16.8±13.3, p<0.02<br><br>Of the 60 stroke patients reporting symptoms of fatigue, no differences in demographics, stroke-related characteristics and stroke-related disability were found compared with the 28 stroke patients without symptoms of fatigue.<br><br>In the stroke group, GDS score was the only independent factor associated with fatigue.<br><br>Stroke patients were younger compared with controls (mean age: 66.6 vs. 74 years, p<0.001). There were no differences in comorbid medical conditions between groups (HTN, cardiac disease, arthritis, DM, thyroid disease). A higher number of stroke patients were taking antidepressants and antiepileptic drugs.<br><br>The frequency of depression (GDS≥11) was higher in the stroke group (40% vs. 14%, p=0.001). |

## Treatment for Post-Stroke Fatigue

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **McGeough et al. 2009**<br><br>**UK**<br><br>**Cochrane Review** | NA | Results from 3 RCTs (n=1,254) were included.<br><br>Subjects included outpatients (n=83) with post-stroke emotional disturbances, a mean of 14 months after stroke onset (n=1), subjects (n=831) with a variety of chronic disease conditions who may/may not have suffered from fatigue at study entry (n=1) and 31 women in the acute stage of SAH who may or may not have suffered from fatigue. | Treatment contrasts included: fluoxetine vs. placebo, (n=1), chronic-disease self-management program (delayed vs. immediate participation, n=1) and tirilazad mesylate vs. placebo for 10 consecutive days (n=1). | Pooled analyses were not possible.<br><br>Fatigue was the primary outcome in one study and a secondary outcome in two. | In the trial that examined fluoxetine specifically as a treatment for post-stroke fatigue, there were no significant differences in the number of patients with fatigue at 3 or 6 months (details presented below).<br><br>In the trial examining the chronic disease management program (detailed below), the authors acquired data reporting on the subset of 125 patients with stroke in the trial. The mean fatigue scale change scores (1-5) at 6 months were 0.246 for controls and 0.087, indicating that fatigue became worse for wait list controls, although the difference was not significant (p=0.253).<br><br>In the trial examining tirilazad mesylate in women who survived and could be assessed for fatigue at 3 months, significantly fewer patients in the intervention group reported debilitating fatigue (4/9 vs. 9/9, p<0.01). |
| **Zedlitz et al. 2013**<br><br>**Netherlands**<br><br>**RCT** | CA: ☑<br><br>Blinding patient: ☒ assessor: ☑<br><br>ITT: ☑ | 83 community dwelling individuals with severe fatigue >4 months post stroke.<br><br>**Exclusion criteria**: age <18 or >70, non-independent ambulation, severe cognitive deficits, and severe comorbidity, including depression. | 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, | **Primary outcomes:** The Checklist Individual Strength-fatigue subscale (CIS-f) and the Fatigue Self-Observation List (SOL-f)<br><br>**Secondary outcomes:** The Hospital Anxiety and Depression Scale, the Stroek-Adapted Sickness Impact Profile 30, and the 6-Minute Walk Test<br><br>**Timing of assessment:** Baseline, at the end of treatment, and at 6-month | Significant main effects of time were observed for all primary and secondary outcomes, except pain and anxiety. No significant group differences or interaction effects of time with group were reported, except for the 6-minute walk test for which both group and interaction effects were reported.<br><br>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), as compared to those in the CO group (57.9% vs. 24.4%, p=0.002).<br><br>**Lost to follow-up:** COGRAT=13.2%, CO=22.2% |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | which consisted of treadmill walking, strength training, and homework assignments. | follow-up. | |
| **Clarke et al. 2012**<br><br>**New Zealand**<br><br>**RCT** | CA: ☒<br><br>Blinding<br>patient: ☒<br>assessor: ☒<br><br>ITT: ☒ | 19 patients with fatigue ≤18 months post stroke.<br><br>Patients were excluded if they had significant impairments precluding participation, were medically unstable, or had another condition that could impact results. | 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).<br><br>**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.<br><br>**Timing of Assessment**: baseline, post-intervention and 3-month follow-up. | 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. |
| **Karaiskos et al. 2012**<br><br>**Greece**<br><br>**RCT** | CA: ☒<br><br>Blinding<br>patient: ☒<br>assessor: ☒<br><br>ITT: ☒ | 60 patients diagnosed with post-stroke depression following a first-ever stroke within 12-months of study recruitment.<br><br>**Exclusion criteria**: history of a major psychiatric disorder, atherosclerotic disease or history of angioplasty/bypass surgery, another major medical illness, degenerative and progressive neurological disease, or severe cognitive impairment. | 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).<br><br>**Treatment Duration:** 3 months. | Fatigue was assessed using the Fatigue Severity Score (FSS). Additional measures included the Mini-Mental State Exam, the modified Rankin Scale, and the Hamilton Rating Scale for Depression and Anxiety.<br><br>**Timing of assessment:** 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.<br><br>Mean FSS scores from baseline to study end:<br>Duloxetine: 4.5 (1.4) to 3.7 (1.1)<br>Citalopram : 4.5 (1.5) to 3.9 (1.3)<br>Sertraline: 4.6 (1.6) to 4.0 (1.4) |
| **Johansson et al. 2012**<br><br>**Sweden**<br><br>**RCT** | CA: ☒<br><br>Blinding<br>patient: ☒<br>assessor: ☒ | 29 patients, 18 with stroke and 11 with TBI, with mental fatigue.<br><br>**Exclusion criteria:** stroke/TIA <12 months prior to recruitment, age <30 or | Participants were randomized to receive a Mindfulness –Based Stress Reduction (MBSR; n=15) program or to a wait list control group (n=14). The | **Primary outcome**: the Mental Fatigue Scale (MFS).<br><br>**Secondary outcomes**: the Comprehensive Psychopathological Rating | As compared to those in the wait-list control group, 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 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | ITT: ☒ | >65, significant comorbidity, and significant cognitive impairment. | 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. | Scale, the WAIS-III digit symbol-coding and digit span subscales, and the Trail Making Test.<br><br>**Timing of assessment**: baseline and post-intervention. | 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 ($p<0.01$).<br><br>**Lost to follow-up**: 20% in the active treatment group. |
| **Brown et al. 2011**<br><br>**USA**<br><br>**RCT**<br>***Sleep Apnea Treatment after Stroke (SATS)*** | CA: ☒<br><br>Blinding<br>patient: ☑<br>assessor: ☑<br><br>ITT: n/a | 54 patients were eligible to participate and were recruited from an inpatient neurology service.<br><br>Inclusion criteria: ischemic stroke within the previous 7 days, with a mRS score >1 and testing 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. | 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).<br><br>Assessments were conducted at baseline and at the end of treatment. | At 3 months, the median (IQR) scores for patients in the active and sham groups were:<br>FSS: 2.6 (2.0, 4.1) vs. 2.4 (1.4, 3.0)<br>ESS: 8 (6,9) vs. 7 (4,10)<br>PHQ-9: 5 (4,6) vs. 2 (2,3)<br>BI: 95 (90,100) vs. 100 (95, 100)<br><br>(no inferential statistics are reported as the trial was designed as a feasibility study)<br><br>**Lost to follow-up**: active CPAP, n=7, sham CPAP, n=6. |
| **Choi-Kwon et al. 2007**<br><br>**South Korea**<br><br>**RCT** | CA: ☒<br><br>Blinding<br>patient: ☑<br>assessor: ☑<br><br>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.<br><br>Patients with SAH or TIA, MMSE score ≤23, severe communication difficulties, and those with a history of pre-stroke depression, were excluded. | 83 patients were randomized to receive 20 mg/day of fluoxetine (n=40) or placebo, (n=43) for 3 months. | **Primary outcomes:**<br>Fatigue (10- point VAS), Fatigue Severity Scale (9-items, each scored on a 7-point Likert Scale, with higher scores indicating more severe fatigue).<br><br>**Secondary outcomes:**<br>+/- of: depression, (based on Beck Depression Inventory score>13) post-stroke emotional incontinence (patient/relative reporting 2+ episodes of inappropriate laughing or | At baseline, the number of patients in the fluoxetine and control groups with depression, excessive laughing, crying and anger were:<br>12 vs. 20, p=ns, 29 vs. 30, p=ns, 9 vs. 7, p=ns, and 26 vs. 30, p=ns<br><br>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.<br><br>The percentage change in mean (±sd) VAS scores at 6 months for patients in the fluoxetine and control groups were: -11.9±40.0 vs. -8.1±31.0, p=ns |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | crying), post-stroke anger proneness (post stroke Spielberger Trait Anger Scale score >pre-stroke score).<br><br>Assessments were conducted at baseline, 3 and 6 month. | 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.<br><br>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).<br><br>Adverse events: No reporting . |
| **Lorig et al. 2001**<br><br>**USA**<br><br>**RCT** | CA: ☒<br><br>Blinding patient: ☒ assessor: ☑<br><br>ITT: ☒ | 1,140 subjects > 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. | 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).<br><br>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.<br><br>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.<br><br>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.<br><br>There were significant improvement from baseline to 1 year in the number of ER/MD visits, disability, health distress, and self-efficacy.<br><br>There were significant improvements from baseline to 2 years in the number of ER/MD visits, health distress, and self-efficacy. |

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