CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Rehabilitation, Recovery and Community Participation Following Stroke

Part Three: *Optimizing Activity and Community Participation following Stroke*

Evidence Tables

Post-Stroke Fatigue

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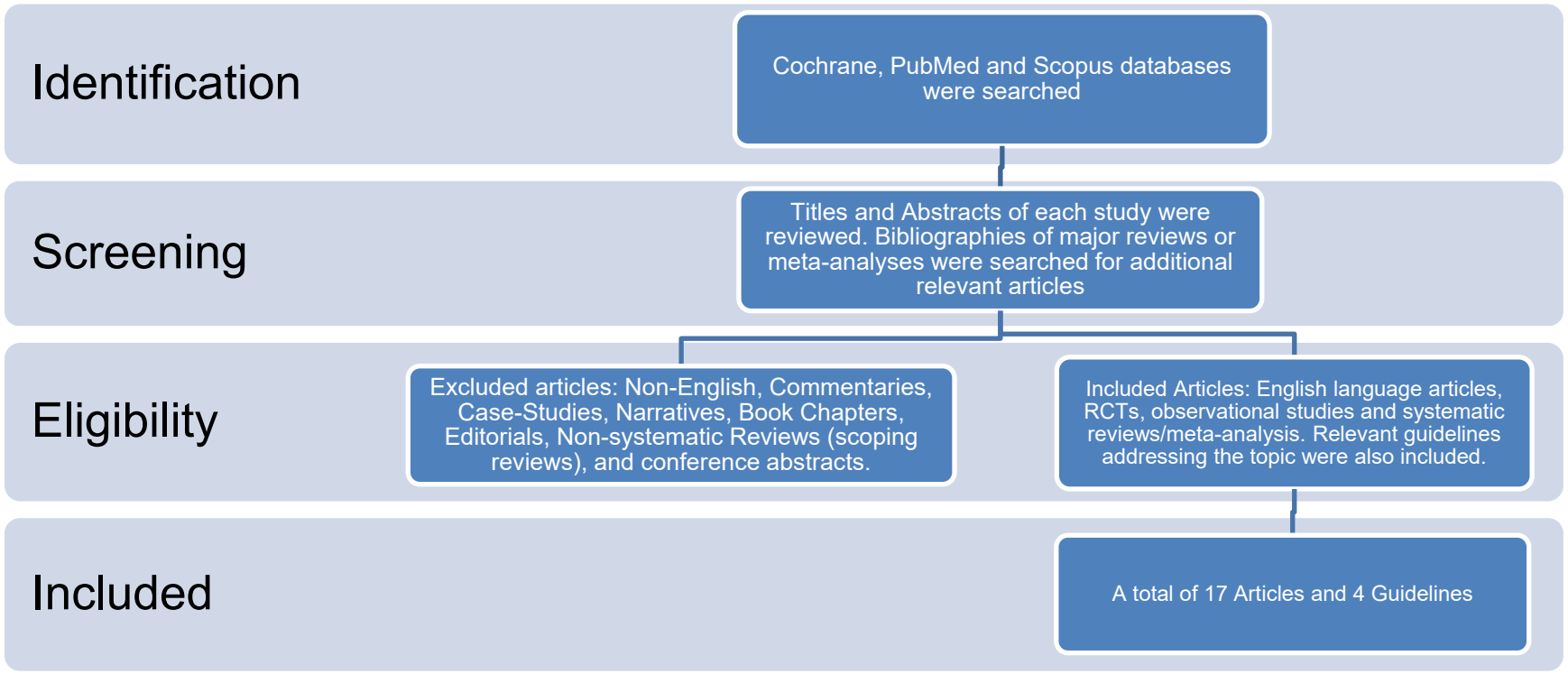
Search Strategy



Cochrane, PubMed and Scopus databases were searched using terms such as [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 17 articles and 4 guidelines were included.

Published Guidelines

Guideline	Recommendations
National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. **Available at:** www.strokeguideline.org. **(selected)**	People with post-stroke fatigue should be referred to appropriately skilled and experienced clinicians as required, and should be considered for the following approaches, whilst being aware that no single measure will be effective for everyone: – building acceptance and adjustment to post-stroke fatigue and recognising the need to manage it; – education on post-stroke fatigue for the person with stroke, and their family/ and carers; – using a diary to record activities and fatigue; – predicting situations that may precipitate or exacerbate fatigue; – pacing and prioritising activities; – relaxation and meditation; – rest; – setting small goals and gradually expanding activities; – changing diet and/or exercise (applied with caution and tailored to individual needs); – seeking peer support and/or professional advice; – coping methods including compensatory techniques, equipment and environmental adaptations
National Institute for Health and Care Excellence **Stroke Rehabilitation in Adults Clinical guideline. 2023** https://www.nice.org.uk/guidance/ng236	1.7.1 Consider a standardised assessment for fatigue in people after stroke in the early stage of their rehabilitation programme and at their 6-month stroke review. [2023] 1.7.2 Consider 1 of the following for the assessment: • the Fatigue Severity Scale • the Fatigue Assessment Scale • the Modified Fatigue Impact Scale. [2023]
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.
Clinical Guidelines for Stroke Management 2022. Melbourne (Australia): National Stroke Foundation. Section 6. Managing complications	Consensus-based recommendations • Therapy for stroke survivors with fatigue should be organised for periods of the day when they are most alert. • Stroke survivors and their families/carers should be provided with information, education and strategies to assist in managing fatigue.

Guideline	Recommendations
	• Potential modifying factors for fatigue should be considered, including avoiding sedating drugs and alcohol, and screening for sleep-related breathing disorders and depression. • While there is insufficient evidence to guide practice, possible interventions could include cognitive behavioural therapy (focusing on fatigue and sleep with advice on regular exercise), exercise and improving sleep hygiene.

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
Zhan et al. 2023 **China** **Systematic review & meta-analysis**	The overall quality of included studies was assessed as medium based on the Joanna Briggs Institute Critical Appraisal Instrument	66 observational studies including 11,697 participants with ischemic or hemorrhagic stroke, who were assessed for fatigue using a validated scale. Mean age ranged from 40.1 to 74.8 years, and the mean time since stroke ranged from 3 days to 10.6 years.	Pooling of data from included studies.	**Primary outcome:** Prevalence of fatigue	The global pooled prevalence of PSF was 46.79% (95% CI 43.41%–50.18%). The Fatigue Severity Scale was, by far, the most common instrument used (47.44%). Prevalence of PSF was 46% in 41 studies where timing of fatigue was ≤12 months vs. 50.3% in 21 studies with assessment >12 months. The prevalence of PSF was higher in participants with depression (48.2% vs. 42.2%) and in women (53.2% vs. 45.0%). The odds of PSF were significantly higher in women (OR=1.41, 95% CI 1.16– 1.72)
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	**Primary outcome:** 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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%.
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.
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.
Glader et al. 2002	NA	5,189 patients who were alive 2 years following	Patients were surveyed by mail questionnaire 2 years	**Primary outcome:** Fatigue was assessed by	Survey response was 79% (n=4,023).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sweden **Prospective study**		stroke, included in the Riks-Stroke national stroke registry.	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.	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.	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**	7 trials were at high risk of bias for failure to conceal the randomization schedule and 6 trials were at high risk of bias for not using intention-to-treat analyses.	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 6 trials (7 comparisons with 244 participants, of which 4 were pharmacological, and 2 non-pharmacological), treatment was associated with a significant reduction in fatigue scores (WMD= -1.07, 95% CI -1.93, -0.21, p=0.014). The effect was larger for pharmacological trials (WMD=SMD -1.23, 95% CI -2.40 to -0.06, 4 trials, n=209; GRADE: very low) compared with non-pharmacological trials (WMD=-0.68, 95% CI -1.37 to 0.02, 2 trials, n=35; GRADE: very low) *Trials not designed to treat fatigue* No pooled analyses were conducted. No intervention was associated with a significant reduction in PSF scores after treatment.

Non-Pharmacological Treatment for Post-Stroke Fatigue

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Komber et al. 2023 **UK** **Systematic review & meta-analysis**	Methodological quality was assessed in 10 trials using the Cochrane RoB tool. Of these, 5 were at low risk of bias across all 5 domains.	13 RCTs, including 484 participants with post-stroke fatigue. Mean age was 62 years, 59% were men. Mean time since stroke was 33.4 months. Data were available in abstract form only in 3 trials.	Trials compared transcranial direct current stimulation (tDCS, n=2), psychological therapies +/- cognitive behavioral therapy (n=5), group psychoeducational therapy (n=1), mindfulness-based strategies (yoga, body scan, n=2) and misc strategies (heart rate variability training through biofeedback, vestibular training and horticultural therapy, n=3). Control conditions included sham therapy, usual care, no therapy, conventional rehabilitation and education. Duration of treatment was not reported.	**Primary outcome:** Fatigue severity at the end of intervention	Mean fatigue severity scores were significantly lower in the intervention group at the end of treatment (SMD=−0.57, 95% CI−0.87 to −0.28, 9 trials, 310 participants). Nonpharmacological therapies were not associated with significant improvement in measures of fatigue assessed at the end of follow-up, which ranged from 6 to 24 weeks (SMD= -0.36, 95% CI -0.83 to 0.10, 6 trials, 112 participants). GRADE: low In subgroup analysis, brain stimulation and physical therapies demonstrated the largest effect sizes.
Mead et al. 2022 **UK** **RCT** ***Post stroke intervention trial in fatigue (POSITIF)***	CA: ☑ Blinding patient: ☒ assessor: ☑ ITT: ☑	76 participants living in the community who had sustained a stroke between 3 months and 2 years previously and who answered yes to 2 questions "*Do you feel tired all the time or get tired very quickly since your stroke"*? and '*Would you like additional help and support for this"*? Mean age was 66.7 years, 57% were men. Mean time since stroke was 10 months.	Participants who were sent an invitation, were eligible and who returned a consent form and screening questionnaires were randomized to an intervention group + a Stroke Association leaflet about fatigue, or to the control group (Stroke Association leaflet only). The intervention consisted of 6 telephone calls (each up to 1 h) conducted over 12 weeks, then a 'booster' call 2-4 weeks later	**Primary outcome:** Feasibility **Secondary outcomes:** Fatigue Assessment Scale (FAS), Patient Health Questionnaire (PHQ)- question 9; Generalised Anxiety Disorder (GAD)-7, Stroke Impact Scale-short form, Euroqol 5D-5L, return to work Assessments were conducted at baseline, 4	At 6 months, there was no significant difference between the groups in mean FAS change score (−0.619, 95% CI −4.9631 to 3.694). The scores in both groups improved over time, declining from 28.9 to 24.2 in the intervention group and from 30.1 to 25.0 in the control group. At 6 months, there was no significant difference between the groups in mean PHQ-9 change score (−0.247, 95% CI −2.935 to 2.442). The scores in both groups improved over time, declining from 9.4 to 6.6 in the intervention group and from 10.6 to 7.1 in the control group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			providing cognitive behaviour therapy, delivered by nurses or a physiotherapist.	and 6 months	At 6 months, there was no significant difference between the groups in mean GAD-7 change score (−0.178, 95% CI −3.823 to 3.467). The scores in both groups improved over time, declining from 6.4 to 4.4 in the intervention group and from 6.8 to 5.4 in the control group. There were no significant differences in mean change scores for any of the other outcomes. There were 8 dropouts/losses to follow-up in the intervention group.
Nguyen et al. 2019 **Australia** **RCT**	CA: ☑ Blinding patient: ☒ assessor: ☑ ITT: ☑	15 participants with post-stroke fatigue (FSS ≥4) and/or poor sleep. Mean age was approximately 49 years, 73% were men. Mean time since stroke was 27 months.	Patients were randomized to receive cognitive behavioural therapy (CBT) emphasizing specific napping schedules and re-organising activity levels as a means of energy conservation in addition to pacing and graded activity exposure (n=9) or treatment as usual (TAU, n=6) for 2 months.	**Primary outcome:** Fatigue Severity Scale (FSS-7) **Secondary outcomes:** Brief Fatigue Inventory (BFI), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), Hospital Anxiety & Depression Scale (HADS), Physical Component Summary of SF-36 (PCS) Assessments were conducted at baseline, 2 months (post-treatment) and 4 months (follow-up)	At the end of the intervention and at 4-month follow-up, there was significantly greater decline in the mean FSS-7 score in the CBT group (mean difference in Δ=1.74, 95% CI 0.70 to 2.77 and 1.92, 95% CI 0.24 to 3.60, respectively). At the end of the intervention and at 4-month follow-up, there was significantly greater decline in the mean PSQI score in the CBT group (mean difference in Δ= 2.27, 95% CI 0.71 to 3.82 and 2.46, 95% CI 0.29 to 4.64, respectively. At the end of the intervention and at 4-month follow-up, there was significantly greater decline in the mean HADS-D score in the CBT group (mean difference in Δ= 4.33, 95% CI 1.71 to 6.95 and, 4.67, 95% CI 1.35 to 7.99, respectively). There was no significant difference in mean change on BFI scores at the end of intervention, or at 4-month follow-up. There was a significant difference in mean change scores at the end of the intervention favouring the CBT group for ISI and PCS scores.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
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.
Zedlitz et al. 2012 **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	**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 Stroke-Adapted Sickness Impact Profile 30, and the 6-Minute Walk Test	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%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			additionally received 24, 2-hour sessions of graded activity training, which consisted of treadmill walking, strength training, and homework assignments.	**Timing of assessment:** Baseline, at the end of treatment, and at 6-month follow-up.	
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 for Post-Stroke Fatigue

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Chu et al. 2023 **UK** **Systematic review and meta-analysis**	Overall risk of bias was assessed as high or having some concerns	10 RCTs including 600 participants with post-stroke fatigue. 6 RCTs were identified including 386 participants that have been completed but not yet published and 6 RCTs are ongoing.	In the 10 completed trials (11 comparisons), pharmacological intervention(s) were compared with placebo or usual care. Active interventions included Fluoxetine (n=1), -OSU6162 (n=3), citicoline (n=1), Astragalus membranaceus (n=1), Modafinil (n=2), Peiyuan Huanwu Decoction (n=1), Xiao Xuming Decoction (n=1) and qi-supplementing dominated Chinese materia medica (n=1) The duration of treatment ranged from 28 days to 3 months. Duration of follow-up ranged from 8 weeks to 12 months in 5 trials with follow-up.	**Primary outcome:** Fatigue severity **Secondary outcomes:** Health-related quality of life, disability, level of dependence, death, return to work, mood, anxiety, apathy, daytime sleepiness, cost-effectiveness of the interventions, adverse effects	Pooling data from 10 trials, pharmacological interventions were associated with a significant reduction in fatigue scores at the end of treatment (SMD= −0.80, 95% CI −1.29 to −0.31), but not at follow-up including the results from 4 trials, including 265 participants (SMD= −0.14, 95% CI −0.38 to 0.10). No pooled analyses were conducted on any of the secondary outcomes due to lack of data.
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-Specific Quality of Life (SSQoL) scale Assessments were conducted at baseline, 6	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. There were 12 adverse events (modafinil=5, placebo=7), but no serious adverse events.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				weeks, 7 weeks (1-week after wash-out period) and at the end of the second 6-week treatment period.	
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, Barthel Index 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**	CA: ☒ Blinding patient: ☑	112 consecutive patients attending an outpatient clinic, an average of 14.5 months following reporting	83 patients were randomized to receive 20 mg/day of fluoxetine (n=40) or placebo, (n=43) for 3	**Primary outcomes:** Fatigue (10- point VAS), Fatigue Severity Scale (9-items, each scored on a 7-	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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	assessor: ☑ ITT: ☑	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 excluded.	months.	point Likert Scale, with higher scores indicating more severe fatigue). **Secondary outcomes:** Presence/absence of depression, (based on Beck Depression Inventory score>13) post-stroke 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.	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 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).

Abbreviations

CA: Concealed Allocation	CI: Confidence Interval
CPSP: Central Post Stroke Pain	IQR: Interquartile Range
ITT: Intention to treat	MD: Mean difference
MMSE: Mini Mental State Examination	N/A: Not Assessed
NRS: Numerical Rating Scale	OR: Odds Ratio
RCT: Randomized Controlled Trial	VAS: Visual Analogue Scale
WMD: weighted mean difference	

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