Question 51 evidence tables

Question 51: What are the effects of different management strategies for post-stroke fatigue?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

PSF = post-stroke fatigue, SSRI = selective serotonin reuptake inhibitor, FAS = Fatigue Assessment Scale, BHT = Buyang Huanwu Tang, FSS = Fatigue Severity Scale, tDCS = transcranial direct current stimulation, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
760	S. Wu et al (2015). Interventions for post-stroke fatigue. Cochrane Database of Systematic Reviews. 7.	Setting: mainly outpatients, some inpatients. Design: Cochrane systematic review of 12 RCTs with meta-analysis to determine the effects of interventions to treat or prevent PSF (and other outcomes). Participants: 703 adults (aged ≥18 years) with a clinical diagnosis of stroke. It was not necessary for participants to have fatigue at recruitment. All were ≥3 months post stroke.	Intervention types: - pharmacological (e.g. antidepressants, wakefulness stimulants), - psychological (e.g. cognitive behavioural therapy, education) - physical training (e.g. graded physical training, aerobic exercise). Comparisons between: - an intervention and a control (placebo, usual medical care or wait-list). - two or more different interventions,	Fatigue at the end of treatment, measured as: - the proportion of people with fatigue - the mean severity of fatigue - both	High quality studies showed no benefit of the following categories of interventions for the treatment of PSF: - antidepressants/ other psychostimulants, - psychological interventions, - physical training, - traditional Chinese therapies, - other interventions. There were no trials primarily investigating the efficacy in preventing PSF. In general, no severe adverse effects were reported for the included interventions.	**++** High quality review, however most studies included were small, heterogeneous, and some had a high risk of bias. There are insufficient data to draw any firm conclusions about whether or not interventions included were effective to treat or prevent PSF.

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			with or without a control. - different doses or intensity of the same type of intervention, with or without a control.			
760	S. Wu et al (2015). Interventions for post-stroke fatigue. Cochrane Database of Systematic Reviews. 7.	Systematic review and meta-analysis Design: RCTs Population: Stroke	Intervention: pharmacological interventions (e.g. antidepressants, wakefulness stimulants), psychological interventions (e.g. cognitive behavioural therapy, educational programme) and physical training (e.g. graded physical training, aerobic exercise)	Outcomes: Fatigue Secondary outcomes • Health-related quality of life (e.g. Short Form-36) • Disability (e.g. Barthel Index score) • Dependence (e.g. modified Rankin scale; mRS) • Death • Cost effectiveness Comprehensive search, including grey literature	12 trials N=8 (455 participants) primarily intended to treat PSF (Choi-Kwon 2007; Clarke 2012; Guo 2012; Gurak 2005; Johansson 2012a; Johansson 2012b; Zedlitz 2012; Zhou 2010) N=0 primarily intended to prevent fatigue after stroke N=4 (248 participants) reported fatigue as an outcome (Brown 2013; Karaiskos 2012; Ogden 1998; Lorig 2001) Heterogenous study populations, interventions (n=7) & outcomes RoB: low risk of bias n=2 (Choi-Kwon 2007; Johansson 2012a) unclear n=1 (Guo 2012) high risk of bias n=5 (Clarke 2012; Gurak 2005; Johansson 2012b; Zedlitz 2012; Zhou 2010)	**++** High quality

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					Of the four trials not primarily intended for PSF: low risk of bias: n=2 (Brown 2013; Ogden 1998) high risk of bias n=2 (Karaiskos 2012; Lorig 2001) Meta-analysis trials with a control arm n=6 (seven comparisons; 244 participants) fatigue severity was lower in the intervention group compared with the control group (pooled SMD -1.07, 95% CI -1.93 to -0.21), with significant heterogeneity between trials (I^2 = 87%, df = 6, P value < 0.00001 for heterogeneity)	
758	L. A. Legg et al (2019). Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database of Systematic Reviews. 11.	Setting: range of different countries and settings. Design: Cochrane systematic review of 63 RCTs with meta-analysis to determine if SSRIs are more effective than placebo or usual care at improving outcomes (incl. fatigue) in people less than 12 months post-stroke, and to determine whether treatment with SSRIs is associated with adverse effects. Participants: 9138 participants with a clinical diagnosis of stroke whom had been given SSRI ≤ 1 year post stroke.	Any drug classified as a Selective Serotonin Re-uptake Inhibitors (SSRIs), any dose or mode of delivery, given for any duration and for any reason. Comparator arm could include usual care or placebo.	Any outcome assessing fatigue.	Analysis reported here limited to studies at low risk of bias. Of these, only one study (FOCUS Trial Collaboration 2018) involving N=3127 (Experimental N=1564; Control N=1563) reported fatigue. - Experimental group: 20 mg fluoxetine orally 1x per day for 6 months - Comparator: matching placebo orally 1x per day for 6 months. Fatigue was measured using the SF-36 vitality score. Outcome: no difference in fatigue between the groups.	**++** High quality review, however only one high quality RCT reporting on fatigue. The FOCUS trial was UK based, including a representative sample.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		About half the trials required participants to have depression to enter the trial.				
758	L. A. Legg et al (2019). Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database of Systematic Reviews. 11.	Setting: Design: Cochrane SR&MA; 63 trials (9168 participants) Subjects: 9168 ischaemic or haemorrhagic stroke survivors at any time within the first year of stroke onset. ~50% of trials required participants to have depression to enter the trial.	Any drug classified as a Selective serotonin reuptake inhibitors (SSRI), (e.g. fluvoxamine, fluoxetine, sertraline, citalopram and paroxetine) at any dose, for any period, and for any indication. The duration, drug, and dose varied between trials. The comparator arm could include usual care or a placebo. Excluded: RCTs that combined an SSRI with another active treatment and compared with the active treatment alone.	Included trials collected data on at least one Primary outcome (independence and or disability score at the end of treatment) independence typically measured using the modified Rankin Scale (mRS), Disability Measures included, but were not limited to, Barthel index (BI) or Functional Independence Measure (FIM)) Secondary outcomes (impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, adverse events and leaving the trial early).	Only 3 RCTs were at low risk of bias. Meta-analysis of low risk of bias trials indicated that SSRIs do not improve recovery from stroke. Potential improvements in disability only identified in analyses which included trials at high risk of bias. Of the high-quality trials, only FOCUS reported fatigue (FOCUS Trial Collaboration 2018). (n=3127): Fluoexetine (n=1564); placebo (n=1563). This was measured using the SF-36 vitality score. There was no difference in fatigue between the groups. SSRIs reduced the risk of future depression but increased the risk of problems with the digestive system.	**++** No evidence to support the use of SSRIs to reduce fatigue after stroke
759	Mead et al (2020). Fluoxetine for stroke recovery: Meta-analysis of randomized controlled trials. International Journal of Stroke 15: 4.	Setting: no restrictions. Design: To determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to	Intervention: any dose of fluoxetine, any mode of delivery, given for any duration. Comparator: usual care or a placebo. Excluded studies	Fatigue and other outcomes (not reported here).	13 trials, N=4145 The only study examining the effects of fluoxetine on fatigue is the FOCUS trial (see elsewhere in this evidence table)	**++** High quality review Main limitation: Little information on participant characteristics

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	365-374	have mood disorders at randomization reduced disability, dependency, neurological deficits and fatigue; improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects. Participants: Stroke in the previous year, excluding trials requiring patients to have a mood disorder at randomization.	comparing fluoxetine plus another ''active treatment'' versus ''active treatment: alone, because of possible interactions.			
759	Mead et al (2020). Fluoxetine for stroke recovery: Meta-analysis of randomized controlled trials. International Journal of Stroke 15: 4. 365-374	Design: Meta-analysis of RCT's Subjects: From searches done in study 3414 references of which 499 full texts were assessed for eligibility and 6 new RCT's added to 7 trial identified from Cochrane review (total: 13 trials, n = 4145) Participants: Searches in 2018 with primary outcomes being dependence and disability.	MA excluded trials requiring pts to have a mood disorder at randomisation. Types of intervention: any dose of fluoxetine, any mode of delivery, given for any duration. Comparator arm was usual care or a placebo and studies were also excluded comparing fluoxetine plus another' active treatment' versus 'active treatment': alone, because of the possible interactions. Duplicate references were removed using software, Titles and abstracts scrutinised. Full texts of potentially relevant articles were	Trial sought to determine whether fluoxetine, at any dose, given within the 1st year post stroke to pts who did not have to have mood disorders at randomisation, reduced disability, dependency, neurological deficits, and fatigue and improved motor function, mood and cognition.	No difference between groups for co-primary outcomes of dependency and disability, fluoxetine was associated with better neurological scores at the end of treatment, better depression scores and fewer diagnosis of depression although the effect sizes were all small. Ultimate data do not support the routine prescription of fluoxetine early after stroke in order to reduce dependency and disability. But may be considered for small effects on depression. 6 new trials added (n=3710) added to 7 eligible trials (n=435). Total 13 completed trials n=4145. Outcome : Independence and disability at end of treatment – 3 trials (n=3249) reported	**+** acceptable. There are some limitations at study and outcome level: only 4 trials were of high methodological quality, not all had been registered prospectively or reported the same outcomes. Different scales were used for the same outcome and although this MA used SMD to combine data, the interpretation of SMD is not intuitive.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
			retrieved and includion criteria applied		independence. Fixed effects MA found no difference in the proportion independent (36.6% fluoxetine vs. 36.7% control; and no difference in disability. Random effects models demonstrated a small but statistically significant benefit of fluoxetine on disability (SMD 0.34, 0.04 to 0.64, p = 0.03, I = 81%) and a higher RR (RR 1.87 (0.74 to 4.56; p = 0.19, I = 78% Secondary outcomes – fluoxetine associated with better neurological scores 8 trials, n = 803, SMD -0.28(-0.42 to -0.14) !=77%better depression scores and fewer diagnosis of depression but have more seizures also slight excess of bone fractures.	
761	AFFINITY trial collaboration (2020). Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. The Lancet Neurology 19:8 651-660	Setting: 43 hospital stroke units in Australia (n=29), New Zealand (four), and Vietnam (ten). Design: randomised, parallel-group, double-blind, placebo-controlled trial. Participants: Adults (aged ≥18 years) with a clinical diagnosis of acute stroke in the previous 2–15 days, brain imaging consistent with ischaemic or haemorrhagic	Intervention: oral fluoxetine 20 mg capsules for 6 months. Control: matching placebo for 6 months.	Fatigue (vitality subscale of the SF-36) Adverse events Other outcomes not reported here.	N (recruited/ target): 1280/1600 Effects at 6 months: No significant difference in fatigue between groups: Fatigue (vitality subscale of the SF-36), median (IQR): Fluoxetine group: 70.0 (55.0–80.0); Placebo group 70.0 (55.0–80.0); P= 0.36. Adverse effects: Compared with patients in the placebo group, patients in the	**++** High Quality Main limitations: Study underpowered Participants from Australia, New Zealand and Vietnam, generally younger and more independent than a UK stroke population. Lack of inclusion of more participants with severe stroke.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		stroke, a persisting neurological deficit that produced a modified Rankin Scale (mRS) score of 1 or more.			fluoxetine group had significantly more falls (20 [3%] *vs* seven [1%]; p=0・018), bone fractures (19 [3%] *vs* six [1%]; p=0・014), and epileptic seizures (ten [2%] *vs* two [<1%]; p=0・038) at 6 months.	
761	AFFINITY trial collaboration (2020). Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. The Lancet Neurology 19:8 651-660	Setting: Hospital stroke units in Australia, New Zealand and Vietnam Design: Randomised parallel-group double-blind placebo-controlled trial Participants: N=1280 (treatment group N=642; control group N=638) Inclusion criteria: adults ≥18 years with clinical diagnosis of acute stroke within previous 2-15 days, brain imaging consistent with ischaemic or haemorrhagic stroke, and with persistent neurological deficit (Modified Rankin Scale (mRS) score of ≥1) Exclusion criteria: any definite indication for fluoxetine; any contraindication for fluoxetine(e.g.: epilepsy; bipolar disorder; drug overdose; fluoxetine allergy; other meds that could interact with fluoxetine; evidence of hepatic impairment, renal impairment, or hyponatraemia); unlikely to be	Intervention group: 1 x 20mg fluoxetine capsule (given orally or, if swallow compromised, via enteral tube feed) per day for 6 months Control group: 1 x identical placebo capsule (given orally or, if swallow compromised, via enteral tube feed) per days of 6 months	Fatigue measured on vitality subscale of SF-36 (secondary outcome measure) Other outcome measures included but not reported here: Functional status (measured by Modified Rankin Scale (mRS) (Primary outcome measure); survival, depression (PHQ-9), cognition (TICSm), communication, motor function and overall health status (SIS), health-related quality of life (EQ-5D-5L), new diagnosis of depression requiring antidepressants. Trial medication adherence and cessation also assessed.	Intervention group: 636/642 participants received fluoxetine. Control group: 637/638 received placebo. At 6 months by treatment group (Intention to treat population): on vitality subscale of SF-36: Intervention group: median 70.0 (IQR 55.0-80.0); Control group: median 70.0 (IQR 55.0-80.0); p= 0.36, so no significant difference between groups Adverse events: Participants in fluoxetine group had more falls causing injury than in placebo group (p=0.018); more bone fractures (p=0.014) and more epileptic seizures (p=0.038)	**++** High quality review Limitations: As stated by authors: Higher doses of fluoxetine not trialled. Further comments: -No site specific data given.

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		available for follow-up during next 12 months; another life-threatening illness making 12-month survival unlikely; pregnant, breast-feeding or of child-bearing age and not on contraception; enrolled on another clinical trial for medicinal product or device		Adverse events assessed during follow-up Measured at: 6 months Measure by: In Australia and New Zealand, centrally assessed; in Vietnam, assessed by site investigator (blinded)		
762	Hankey et al. (2021). Twelve-Month Outcomes of the AFFINITY Trial of Fluoxetine for Functional Recovery After Acute Stroke: AFFINITY Trial Steering Committee on Behalf of the AFFINITY Trial Collaboration. Stroke 52:8 2502-2509	Setting, Design, Participants: As for the AFFINITY trial	As for the AFFINITY trial	As for the AFFINITY trial	N (analysed): 1097/1280 Effects at 12 months post randomisation: No significant difference in fatigue between groups: Fatigue (vitality subscale of the SF-36), median (IQR): Fluoxetine group: 75.0 (60.0–85.0) Placebo group: 70.0 (60.0–80.0), P= 0.48. Adverse effects: Patients allocated fluoxetine had fewer recurrent ischemic strokes (14 [2.18%] versus 29 [4.55%]; *P*=0.02), and no longer had significantly more falls (27 [4.21%] versus 15 [2.35%]; *P*=0.08), bone fractures (23 [3.58%] versus 11 [1.72%]; *P*=0.05), or seizures (11 [1.71%] versus 8 [1.25%]; *P*=0.64) at 12 months.	**++** High quality Main limitation: As for the AFFINITY trial

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
762	Hankey et al. (2021). Twelve-Month Outcomes of the AFFINITY Trial of Fluoxetine for Functional Recovery After Acute Stroke: AFFINITY Trial Steering Committee on Behalf of the AFFINITY Trial Collaboration. Stroke 52:8 2502-2509	Participants recruited from 43 hospital units in Australia (n-29), New Zealand (4), and Vietnam (10) Design: Pre-planned secondary analysis of AFFINITY trial which was a randomised, double-blind, placebo-controlled clinical trial. Participants: n=1280 randomised to 2 groups - treatment with oral fluoxetine (n=642) and placebo control group (n-638) Inclusion criteria: adults aged ≥ 18 with a clinical diagnosis of acute stroke confirmed by brain imaging within the previous 2-15 days, with a persisting neurological deficit producing a mRS score of ≥ 1. Exclusion criteria: definite need for fluoxetine, or contradiction to fluoxetine, availability for follow-up over 12 months, concurrent life threatening illness, pregnancy/breast feeding or child bearing age not using contraception, enrolled in other clinical trial	Randomisation via a secure, web-based system using a minimalisation algorithm assigned participants to a: (i) treatment group (n-642) who received oral fluoxetine 20mg once a day for 6 months or a (ii) placebo group (n=638) who received visually identical placebo capsules to be taken once a day for 6 months. Participants in Australia and New Zealand were followed up at 180 days (6mth) and 365 days (12mth) by postal questionnaire or telephone by trained staff. Participants in Vietnam were assessed by site investigator at 180 days (6mth) & 365 days (12mth) in hospital, clinic, own residence or telephone email. Proxy assistance to complete assessments was allowed when participant unable.	Secondary outcomes at 12 months (the subject of this paper): Fatigue (rated on the Vitality subscale of the SF-36, whereby higher scores indicate less fatigue) Other secondary measures at 12 months: mRS, mood (PHQ 9 score), cognition (TICSm), communication, motor function, overall health status (SIS), health related QOL (Euro QoL EQ-5D-5L), safety outcomes.	Fatigue score: no statistically significant difference in the scores on the Vitality subscale of the SF-36 in relation to fatigue levels at 12 months between the oral fluoxetine group and the placebo control group participants. (median score for oral fluoxetine 75 v's placebo control 70) p value = 0.48 No significant difference between treatment groups in any of the other secondary efficacy outcomes at 12 months or safety measures, other than lower incidence of ischaemic stroke in the oral fluoxetine group at 12 months follow-up which was deemed to be a chance finding. Attrition rate by 12 month (365 days): Fluoxetine treatment group (n= 606) (5.6% attrition) and placebo group (n=615) (3.6% attrition) Intention to treat analysis included in results.	**++** High quality randomised, double-blind, placebo-controlled clinical trial. Limitations – were not specified by authors in this paper, but were mentioned in parent paper (71) AFFINITY trial eg. failure to recruit more participants with severe disabling stroke, no testing of higher dosage of fluoxetine. Additional possible limitation (suggested by reviewer): -? risk of inaccuracy of assessment score being completion by proxy assistance in some cases. Minimal detail of this process in the paper.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
763	FOCUS Trial collaboration (2019). Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. The Lancet 393:10168 265-274	Setting: 103 hospitals in the UK Design: pragmatic, multicentre, parallel group, double-blind, randomised, placebo-controlled trial. Participants: aged 18 years or older, had a clinical stroke diagnosis, were enrolled and randomly assigned between 2 days and 15 days after onset, and had focal neurological deficits.	Intervention: Fluoxetine 20 mg once daily for 6 months Control: matching placebo orally once daily for 6 months	Fatigue (vitality subscale of the SF-36) Adverse events Other outcomes (not reported here)	Effects: No significant difference in fatigue between groups: Fatigue (vitality subscale of the SF-36), median (IQR). Fluoxetine group: 56.25 (37.50–75.00) Placebo group: 56.25 (43.75–75.00), P= 0.6726 Adverse effects: Significantly more bone fractures in the fluoxetine compared with the control group (45 [2·88%] *vs* 23 [1·47%]; difference in proportions 1·41% [95% CI 0·38–2·43]; p=0·007)	High quality Main limitation: No intention-to-treat analysis for fatigue
763	FOCUS Trial collaboration (2019). Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. The Lancet 393:10168 265-274	Setting: 103 hospitals in the UK Design: pragmatic, multicentre, parallel group, double-blind, randomised, placebo-controlled trial Participants: aged 18 years or older, had a clinical stroke diagnosis, were enrolled and randomly assigned between 2 days and 15 days after onset, and had focal neurological deficits Large exclusion criteria	Fluoxetine 20 mg or placebo were administered to patients orally once daily for 6 months Patients were supplied with 186 capsules. If a patient was unable to swallow capsules and had an enteral feeding tube in place, the capsules were broken open and the contents put down the tube according to accepted methods.	The primary outcome/aim of trial was functional status Fatigue was amongst many potential secondary outcomes and was measured on the Vitality subscale of SF36.	Fluoxetine 20 mg given daily for 6 months after an acute stroke does not significantly improve patients' functional outcome or survival at 6 and 12 months. However, fluoxetine decreased the occurrence of depression. There were no significant differences in any other secondary outcomes at 6 months, including any of the nine domains of the SIS, the Vitality subscale of SF36, and EQ5D-5L Effects on Fatigue: No significant difference in fatigue between groups:	High quality, well randomised, 3,000+ participants, moderate compliance, minimal loss to follow up Fatigue was not main focus of the trial – only a secondary outcome

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					Fatigue (vitality subscale of the SF-36), median (IQR). Fluoxetine group: 56.25 (37.50–75.00) Placebo group: 56.25 (43.75–75.00), P= 0.6726 Adverse effects: Significantly more bone fractures in the fluoxetine compared with the control group (45 [2·88%] vs 23 [1·47%]; difference 1·41% [95% CI 0·38–2·43]; p=0·0070)	
768	Pacheco et al. (2019). Modafinil for poststroke patients: A systematic review. Int J Clin Pract 73:2 e13295	Setting Design Systematic review Participants adults from 14 days poststroke up to 3 months poststroke	Modafinil at any presentation and therapeutic scheme compared with any other intervention, including both pharmacological and non-pharmacological interventions	Fatigue, assessed by the Multidimensional Fatigue Inventory – 20 (MFI-20) or any other validated criteria. Other outcomes (not reported here)	Two RCTs included (N=77 participants): Heterogeneity precluded meta-analysis and study results were presented separately: Bivard et al. (2017): see elsewhere in this evidence table. Poulsen et al.(2015): this study was not selected for the guideline update as it was an exploratory study.	**++** High quality review Studies included in review were small RCTs with very low GRADE quality evidence
768	Pacheco et al. (2019). Modafinil for poststroke patients: A systematic review. Int J Clin Pract 73:2 e13295	Study 1 Bivard (2017) Design- Randomised crossover clinical trial Setting- Australia Subjects- 36 randomised stroke survivors (61% male, 92% ischaemic stroke) Mean age 65 Group 1 Mean age 60 Group 2	Study 1: 6 week follow up Group 1- Modafinil 200mg Group 2- Placebo Study 2: 9 week follow up	Study 1: 6 week follow up -Fatigue with MFI-20, MFI general fatigue dimension, Fatigue Severity Scale. -QoL with Stroke-specific quality of life scale. -Cognition with Montreal cognitive ax.	Some benefit shown when re-assessing fatigue (6 weeks study 1, & 9 weeks study 2 follow up) when using MFI-20 and Fatigue Severity Scale but not when using MFI (general) - benefit seen in 6 wk follow up study but not 9. No benefits seen for all other primary and	**++** High quality syst rv methodology following Cochrane review guidelines, however sample sizes, quality and number of included studies very low hence no firm

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		Study 2 Poulsen (2015) Design- Randomised parallel clinical trial Setting- Denmark Subjects- 41 randomised stroke survivors (46% male, 90% ischaemic stroke) Median age 61 Grp 1 Median age 71 Grp 2	Group 1- Modafinil 400mg/200mg for patients over 65. Group 2- Placebo	-Minor adverse events with count. Study 2: 9 week follow up -Fatigue with MFI general fatigue dimension and Fatigue Severity Scale. -Disability with Modified Rankin Scale, Barthel 100-index, Scandinavian stroke scale. -Major adverse events with count. -Minor adverse events with count. -QoL with stroke-specific QoL scale (sub scores). -Cognition with Montreal cognitive assessment. Results presented as comparisons when able.	secondary measures across both studies.	conclusions given by the authors. More high quality RCT's needed on the topic.
766	Gagnon et al (2020). Amantadine and Modafinil as Neurostimulants During Post-stroke Care: A Systematic Review. Neurocritical Care. 33:1. 283-297	Setting: no restrictions Design Systematic review to describe amantadine (not further reported) and modafinil administration practices post-stroke, identify time and rate of cognitive and functional responsiveness and the incidence of potential adverse effects. Participants: people with stroke	Modafinil	Impact on cognitive or functional outcomes Adverse effects	This review included the studies by: Bivard et al. (2017): see elsewhere in this evidence table. The remaining studies were not relevant for this update as they were either published before 2015, or were exploratory.	- Low quality review Main limitations of the review: limited search, lack of clarity re. independent data extraction, lack of quality appraisal of studies included, non-RCTs included in analysis of effects (therefore not reported here).

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
764	A. Bivard et at (2017). MIDAS (Modafinil in Debilitating Fatigue after Stroke): A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial. Stroke. 48. 1293-1298.	Setting: hospital setting, Australia. Design: single-centre, randomised, double blind placebo-controlled cross-over trial to assess the effects of modafinil after stroke. Participants were randomized 1:1 to modafinil or placebo for the first 6 weeks -> 1 week washout period -> cross-over into the alternate treatment arm for the second 6 weeks. Participants: N=36 with first stroke. Inclusion criteria: age>18 years, time post stroke ≥3 months, score ≥60 across all domains of the multidimen-sional fatigue inventory (MFI-20, indicating significant fatigue). Exclusion criteria: known contraindications to modafinil: renal impairment, causes of other clinically recognised causes of fatigue such as narcolepsy, use of benzodiazepines or antiepileptic drugs and pre-existing depression, dementia, or other neuropsychiatric disease; diagnosed or suspected sleep apnoea. Mean age 63 years (SD 15); baseline MFI 72 (SD 8.7). Mean time post stroke 9 months (range 3–38 months), 61% male, N=33 with ischemic stroke.	Intervention group: 1x 200 mg modafinil tablet per day for 6 weeks Placebo control group: 1x 200 mg rice powder tablet per day for 6 weeks Interventions looked identical.	Measures: - Multidimensional fatigue inventory (MFI) (max. 100 with higher score indicating greater fatigue), [Other measures included but not reported here: - Montreal cognitive - Assessment (MOCA), - Fatigue Severity Scale (FSS), - Depression, Anxiety, and Stress Scale (DASS), - Stroke-Specific Quality of Life (SSQoL) scale.] Drug adherence: monitored through tablet return for each patient in each group. Adverse events: registered by interview through monthly phone calls and review of patient files at each visit. Measured at: - baseline, - in the last week of the first 6-week treatment arm, -after a 1-week washout period, - in the last week of the second 6-week treatment arm.	Target recruitment achieved, no dropouts. Fatigue: statistically significant benefit in favour of the intervention (MFI total score mean difference, −7.38; 95% CI, −21.76 to −2.99; *P*<0.001); FSS mean difference -6.31; 95% CI -10.69 to -1.92; P<0.0048). Adverse events: no serious adverse events. 12 adverse events (modafinil=5, placebo=7), no serious adverse events. Adverse events included: headache (4), nausea (1), anxiety (2), agitation (3), dizziness (2).	**++** High quality

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		Stroke severity: not reported.		Measured by: blinded assessor		
767	Jin et al. (2021). A Systematic Review and Meta-Analysis of the Effects of Herbal Medicine Buyang Huanwu Tang in Patients with Poststroke Fatigue. Evid Based Complement Alternat Med 2021: 4835488	Setting China Design Systematic review and meta-analysis of RCTs and quasi-RCTs Participants: patients with PSH diagnosed using a qualified clinical diagnostic method (such as the Fatigue Assessment Scale [FAS] and the Fatigue Severity Scale [FSS]) or subjective fatigue symptoms	Buyang Huanwu Tang (BHT); herbal medicines	Fatigue Assessment Scale [FAS] Adverse effects	Effects: In the adjunctive BHT group: a statistically significant improvement in the Fatigue Severity Scale score (mean difference −1.49, 95% CI [−2.25, −0.73]) and total clinical efficacy rate (risk ratio 0.11, 95% CI [0.03, 0.41]) compared the non-herbal group. Adverse events were only reported in one study, no serious adverse events occurred.	**+** Acceptable review Studies included were of low quality as they provided insufficient information on: participant characteristics, conventional therapies, adverse events, study methodologies. There was considerable heterogeneity in BHT components and dosages.
773	Y. Su et al (2020). Non-pharmacological interventions for post-stroke fatigue: Systematic review and network meta-analysis. Journal of Clinical Medicine. 9: 3. 621.	Setting: Australia, the Netherlands, China Design: systematic review network meta-analysis of RCTs: pair-wise meta-analyses with a random effects model to synthesise studies comparing intervention with control. Participants: any participants diagnosed with ischemic or hemorrhagic stroke, diagnosed by MRI or CT median age: range 47 to 69 years, disease duration: rang 2 weeks to 27 months.	Intervention group defined as providing additional non-pharmacological interventions based on usual treatment. Types identified: - Community Health Management (CHM, 1 study) - Traditional Chinese Medicine (TCM, 3 studies) - Cognitive Behavioral Therapy (CBT, 2 studies)	Fatigue Severity Scale (FSS)	Population: 777 participants Compared with usual care, the non-pharmacological interventions resulted in a statistically significant reduction in fatigue (MD -1.46, 95% CI -1.58 to -1.35, P<0.001), but heterogeneity was high (I^2=95%). Network meta-analysis did not find any statistically significant differences between the non-pharmacological interventions.	**+** Acceptable quality However, small body of evidence and despite being acknowledged by the authors, methodological limitations were not sufficiently taken into consideration when analysing the findings. Studies were at unclear or high risk of bias: - 8/10 had unclear allocation concealment, - 1/10 studies was at high risk and 8/10 studies were at unclear risk of performance bias (i.e.

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			- Respiratory Therapy (RT) and Music Therapy (MT), 2 studies - Circuit Training (CT, one study) - Hyperbaric Oxygen Therapy (HOT, one study) Control group: treatment 'as usual', including usual treatment, nursing, and rehabilitation.			blinding of participants and staff), - 6/10 studies were at unclear risk of detection bias (i.e. assessor blinding). - 5/10 studies were at high risk of attrition bias (i.e. incomplete outcome data) - 8/10 studies were also at unclear risk of other bias. Main limitations: - No sensitivity analysis was undertaken, despite high heterogeneity - only the FSS was included. RCTs that did not have a usual care control group could not be included.
765	Y. Chen et al (2022). Acupuncture for the Adjunctive Therapy of Post-stoke Fatigue: A Systematic Review and Meta-analysis. Acupuncture and Electro-Therapeutics Research. 47: 1. 115-128	Setting: All studies were undertaken in China. Design: Systematic review of 6 RCTs with meta-analysis to determine the effects of [acupuncture plus conventional rehabilitation] compared with [conventional rehabilitation] on fatigue in people with first stroke. Participants: 426 participants (Treatment group N=213; Control group N=213). Average age ranged from 58-67 years, with more males than females. Mean duration of symptoms: 1.3 – 2.7 months.	Acupuncture: average number of acupoints was 8 (range 2 to 16). The most commonly used five acupoints were: CV6 (Qihai), ST36 (Zusanli), CV4 (Guanyuan), GV20 (Baihui), and SP6 (Sanyinjiao). The most common mix proportion rules of the two acupoints were CV6 (Qihai) and CV4 (Guanyuen), ST36 (Zusanli) and SP6 (Sanyinjiao).	Measures: Fatigue: Fatigue Severity Scale (FSS): pre-specified 'Energy part of QoL'(SS-QOL-E): not pre-specified. Measured at: End of intervention (no follow-up)	Fatigue (6 studies, N=426 with Treatment group N=213; Control group N=213). Statistically significant reduction in fatigue in favour of the Treatment group (MD = -5.45, 95% CI = (-6.75, -4.14), Z= 8.19 (P < 0.001), I^2=38%) Energy (3 studies, N=90 with Treatment group N=90; Control group N=90). Statistically significant increase in energy in favour of the Treatment group (MD = 1.69, 95% CI = (0.27, 3.12), Z = 2.33 (P < 0.02), I^2=89%).	**+** Acceptable quality However, small body of evidence and despite being acknowledged by the authors, methodological limitations were not sufficiently taken into consideration when analysing the findings. All studies were small. Note: only one study had received ethical approval. All 6 studies were affected by risk of bias: - most studies were at unclear risk of selection bias (4/6 unclear random sequence generation; 5/6

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		Time post stroke: not reported. Fatigue level at baseline: not reported. Stroke severity: not reported.	Intervention period ranged from 14-84 days, needle retention time ranged from 30-40 min. per session. Rehabilitation: no information on content or dose.		Note: figures 5-6 seem to have been confused. Adverse events: only one study reported no adverse events.	unclear allocation concealment), - all studies were at risk of performance bias (i.e. unclear blinding of participants and staff), - 5/6 studies were at unclear risk of detection bias (i.e. assessor blinding). - 4/6 were at high risk of attrition bias (i.e. incomplete outcome data) - All 6 studies were also at unclear risk of other bias. There was no sensitivity analysis.
765	Y. Chen et al (2022). Acupuncture for the Adjunctive Therapy of Post-stoke Fatigue: A Systematic Review and Meta-analysis. Acupuncture and Electro-Therapeutics Research. 47: 1. 115-128	Systematic review and meta-anlaysis Design: RCTs only Participants: stroke patients Intervention: acupuncture as an adjunct to rehabilitation Currency: inception to Dec 2020 Language: Chinese and English only Not a comprehensive search string	Intervention: acupuncture plus conventional treatment; no limitation on the number of acupoints, acupuncture methods, positions, courses of treatment, times of treatment Control: conventional treatment, according to stroke rehabilitation guidelines	Fatigue: Fatigue Severity Scale (FSS score)	6 papers included in the meta-analysis Participants: n=426 (n=213 experimental group; n=213 control group) Young: 58- 67 (means) More male than female participants Intervention: acupuncture n=5; electroacupuncture n=1 Time: 14 days: n=3; 28, 56, 84 (all n=1) Selected acupoints (mean): 8 (ranging from 2 to 16) (table 3). Most common: CV6 (Qihai), ST36 (Zusanli), CV4 (Guanyuan), GV20 (Baihui), SP6 (Sanyinjiao)	+ Acceptable

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					Most common mix proportion rules of the two acupoints were CV6 (Qihai) and CV4 (guanyuen); ST36 (Zusanli) and SP6 (Sanyinjiao) (fig 4) Methodologically poor studies FSS: the six studies concluded that therapy as an adjuvant therapy had significant improvement effect on post-stroke fatigue (PSF) [MD = -5.45, 95% CI = (-6.75, -4.14), Z = 8.19 (P < 0.001)] (fig 5) SS-QOL-E: three studies [24-26] concluded that although I^2 = 89% was highly heterogeneous, acupuncture therapy as an adjuvant therapy still had an improvement effect on the energy part of QoL after stroke [MD = 1.69, 95% CI = (0.27,3.12), Z = 2.33 (P < 0.02)] (fig 6)	
771	Dong et al (2021). A randomized controlled trial to explore the efficacy and safety of transcranial direct current stimulation on patients	Setting: hospital in China Design: RCT Participants: Target sample size: N≥23 in each group.	Both groups received usual care. In addition: Experimental intervention: Content: active transcranial direct	Measures and time points: Fatigue Severity Scale (FSS): at baseline, at end of 4-week intervention and at 12 weeks (i.e. 8-week follow-up after intervention end).	Number of participants included in analysis: N=53/60 at 4 weeks, N=45/60 at 12 weeks (i.e. 8-week follow-up after intervention end).	+ Acceptable Participants and assessors were blinded. Main limitations:

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	with post-stroke fatigue. Medicine. 41. e27504.	Total recruited: N=60 (N=30 in experimental group, N=30 in control group.) Inclusion criteria: Age 18-65 y; time post stroke between 3-12 months; Fatigue Severity Score >36. Absence of: significant head displacement, structural damage, extensive brain necrosis, significant pyramidal tract necrosis or thalamic injury, >30% of each lobe damaged within each hemisphere (all verified by MRI); medically stable. Exclusion criteria included: Sedatives, anaesthetics, psychoactive drugs, muscle relaxants, or Na+ and Ca2+ channel blockers; relying on inhalers, contra-indications, epilepsy or seizure history, serious health conditions, local skin lesion/ inflammation, haemostasis, coagulation, or anticoagulation dysfunction; high sensitivity of pain stimulation area, hemiplegia or impaired limb function (Fugl-Meyer scale score <85); aphasia, incomplete clinical data and poor compliance; score ≥10 on the PHQ-9 scale.	current stimulation (tDCS): - Device: MBM-I (Nanchang City, Jiangxi Province, China). - Electrode plate: diameter 5cm. - Electrode location: anode placed on dorsolateral pre-frontal cortex (DLPFC) on the left side of the patients' forehead; cathode on superior margin of the right orbit. - Current intensity: 1.5mA Dose: 20 minutes per session, 1x pday, 6x pweek for 4 weeks. Delivered by: a specialised therapist. Control intervention: Content: sham tDCS, as per Experimental group except that the current was only applied every 15 seconds during the initial phase, with no current output during the intermediate 19.5 minutes of the sham stimulation.	Assessed by: blinded assessor. Adverse reactions, assessed at each treatment session. [Other outcomes assessed but not reported here as not relevant for this topic: Modified Barthel Index (Chinese version) Fugl-Meyer Scale]	After 8* weeks of intervention*, detection rate of post-stroke fatigue was 38.46% (10/26) in the experimental group, vs. 70.37% (19/27) the control group (P=.020). (*this should read 'after 4-weeks of intervention' as the number of participants corresponds to the number present after 4 weeks in the CONSORT diagram). After the 4-week intervention, control group FSS score was significantly higher than experimental group FSS score (P=.012). After the 12-week follow-up (i.e. 8 weeks after intervention end), control group FSS score was significantly higher than experimental group FSS score (P<.001). Adverse reactions: 53.85% (14/26) of participants had mild tingling, 7.69% (2/26) had mild itching (acceptable). No adverse reactions (e.g. burns or nausea). Vital signs remained stable. There is no information on how these AEs compared with the control group.	- Analysis for effect at post-intervention remained sufficiently powered; analysis for effect at follow-up fell short by 1 participant in the control group. - No Intention-to-Treat analysis. - No indication of correction for repeated measures.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
771	X. L. Dong et al (2021). A randomized controlled trial to explore the efficacy and safety of transcranial direct current stimulation on patients with post-stroke fatigue. Medicine. 41. e27504.	Setting: China, hospital Design: RCT Participants: N =60 (treatment group N= 30, control group N =30) (target size ≥ 23 per group). Inclusion: -Stroke onset ≥ 3 months, ≤ 1 year. -male/female 18-65 years - Fatigue Severity Scale score >36. - MRI shows no significant displacement/structural damage/necrosis/thalamic injury; ≤30% damage of each lobe on one side of brain -medically stable, family gave informed consent Exclusions: -on sedatives, anesthetics, psychoactives, Na+ or Ca2+ channel blockers, muscle relaxants - reliant on inhalers - contraindications to use of electrical stimulation - epilepsy/seizure history - medical complications or comorbidities (various listed) - fever - skin injury/inflammation - hemostasis, coagulation or anticoagulation dysfunction - high pain sensitivity -hemiplegia/limb dysfunction (Fugl-Meyer<85) - aphasia - incomplete clinical data	4-week intervention period: -Treatment group and control group both receive basic care/treatment (e.g. control of blood pressure/sugar; positioning; training of joint muscles; stair practice; self-care practice) - Treatment group: Active tDCS (transcranial direct current stimulation): - device is MBM-1 (Nanchang City, Jiangxi Province, China). - anode placed on dorsolateral prefrontal cortex (DLPFC) on left forehead, cathode on superior margin of right orbital. - electrode plate 5 cm diameter. - current of 1.5 mA, 20 mins per session, 1x per day, 6x per week, for 4 weeks. - treated by specialised therapist (not otherwise specified) - Control group: sham tDCS: All as above except:	Primary outcome: Fatigue severity scale (FSS) -carried out at baseline assessment; after 4-week intervention period; at 8th week of follow-up. Adverse reactions assessed during each treatment session. Other outcomes not directly relevant here: Fugl-Meyer movement-function assessment (FMA) Modified Barthel index (MBI) (at baseline and after 4-week intervention)	According to flow diagram: at 4 weeks, treatment group N= 26, control group N= 27 (so total N=53) At 12 weeks (end of 8-week follow-up), treatment group N= 23, control group N= 22 (so total included in analysis N=45)* *however, in text (1st paragraph of results section), stated that at end of 12 weeks (4 weeks treatment and 8 weeks follow-up), final sample size was 53 After 8 weeks of intervention** detection rate of fatigue in control group was 70.37% (19/27) and in treatment group was 38.46% (10/26), significantly lower (P = 0.020) (** not clear if this means at end of 8-week follow-up? But participant numbers suggest they refer to assessment after 4-week intervention period) At 4 week assessment (end of intervention), control group FSS scores were significantly higher than for treatment group (P = 0.012). At 8 week follow-up, control group FSS scores were	+ Acceptable Randomisation appear robust. Treatment and control arms well-balanced. However, some issues: -exclusion of individuals with aphasia or significant hemiplegia -discrepancies/lack of clarity around some figures reported in results (see notes in results column) -analysis based only on participants who completed intervention and follow-up- no method to deal with missing data -sample size dropped below target for control group at follow-up

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		- poor compliance - depression (≥10 on PHQ-9)	- Current input only every 15 secs during initial phase, no current output during intermediate period of 19.5 mins.		significantly higher than for treatment group (P < 0.001). Adverse reactions: 53.85% (14/26) treatment group had mild tingling, 7.69% (2/26) had mild itching. Taken as acceptable. No burns or nausea. Vital signs stable.	
770	E. Byun et al (2021). Brief Psychosocial Intervention to Address Poststroke Depression May Also Benefit Fatigue and Sleep-Wake Disturbance. Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses. 46: 4. 222-231. Also refer to: Kirkness, C. J., Cain, K. C., Becker, K. J., Tirschwell, D. L., Buzaitis, A. M., Weisman, P. L.,McKenzie, S., Teri, L., Kohen, R., Veith, R. C., & Mitchell, P. H. (2017). Randomized trial of telephone versus in-person delivery of a brief	Setting: recruited from six university and community hospitals in the Seattle, WA area Design: pre-planned secondary analysis of 3-arm RCT: - Group 1: Brief psychosocial intervention, delivered in-person - Group 2: Brief psychosocial intervention, delivered over the telephone - Group 3: usual care Participants: (N=100); Group 1 (N=35), Group 2 (N=37), Group 3 (N=28) - Inclusion: age ≥21 years - Hospitalised with ischaemic/ haemorrhagic stroke within past 4 months Clinical depression symptoms (Geriatric Depression Scale Score ≥11)	Brief psychosocial intervention aimed at reducing depression, including a behavioural and a pharmacological component. - Content: Cognitive Behavioural Therapy. Topics: (1) introduction to CBT, pleasant events; (2) scheduling pleasant events; (3) managing depression behaviours: problem-solving; (4) changing negative thoughts and behaviours; (5) problem-solving in depth; (6) review of skills, strategies to maintain skills. Included manuals	Measures: - Fatigue: PROMIS 7-item scale - Sleep disturbance (PROMIS 8-item sleep scale) - Wake disturbance (PROMIS 8-item wake scale) Measured at: - Baseline - 8 weeks (after the 6-week intervention) - 21 weeks after the intervention - 12 months after the intervention Measured by: blinded assessor.	Number of participants included in the analysis: Group 1 (N=30), Group 2 (N=33), Group 3 (N=24) Between baseline and 12 months (all outcomes): Fatigue, sleep disturbance and wake disturbance improved in both intervention groups but not in the usual care group - but there were no statistically significant differences between groups. Wake disturbance: improvement in both intervention groups exceeded the Minimal Clinically Important Difference.	+ Acceptable quality Main limitations: - All participants had clinical depression, therefore findings cannot be generalised beyond this population. - Intervention started within 4 month post-stroke, hence findings cannot be generalised beyond this period. - Study probably underpowered - Attrition 14%, 11%, 14% in groups 1, 2, 3 resp. but no Intention-to-Treat analysis No information on usual care input, which may have confounded the intervention effects.

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	psychosocial intervention in poststroke depression. BMC Research Notes, 10(1), 500. 10.1186/ s13104-017-2819-y		and homework. One session designed for caregivers. - Dose: 6 sessions: 1 hour per week, 6 weeks - Delivered by advanced practice nurses - Delivery mode: Group 1: in person (usually the person's home) - Group 2: by telephone. Usual care: no intervention other than what was provided to both groups. Both groups: - American Stroke Association booklet about stroke recovery and depression - Ongoing medical care, including antidepressant adjustment, from their own provider.			

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770	E. Byun et al (2021). Brief Psychosocial Intervention to Address Poststroke Depression May Also Benefit Fatigue and Sleep-Wake Disturbance. Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses. 46: 4. 222-231.	Setting: Participants were recruited from 6 university and community hospitals in the Seattle, WA area, USA. Design: Pre-planned secondary analysis of RCT efficacy trial Participants: n=100 participants aged 21 or over, hospitalized for ischaemic or haemorrhagic stroke within the past four months and clinical depression symptoms which scored ≥ 11 on The Geriatric Depression Score at time of screening.	Participants were randomised into one of 3 arms: Intervention arms– 'Brief psychosocial-behavioural intervention' delivered by Advanced practice nurses.1 hour per week for 6 weeks to either in-person (n-35) or by telephone consultation (n=37). Participants in both the intervention groups were also given written materials from the American Stroke Association, ongoing medical care from their own provider and antidepressant adjustment as determined by their provider. Usual care (control) - Written information from the American Stroke Association was provided and regular appointments with a primary care provider (n=28). Antidepressants were prescribed and adjustments made as per the intervention arms of the study.	(a) PROMIS seven item Fatigue Scale (Cook et al 2012) which measures; perceived tiredness, exhaustion, lack of energy, and impact of function in the past 7 days was administered to those n=100 patients who were eligible and participated in the study. This was scored on 4 occasions: on entry to the study, 8 weeks, 21 weeks and 12 months post-treatment. The MCID (minimal clinically important difference) score for the seven item fatigue T score was also measured in this study. (b) The PROMIS eight item Sleep Scale which focuses on: perceptions of quality, depth and restoration associated with sleep, perceived difficulties with getting to sleep or staying asleep, and perceptions of adequacy and of satisfaction of sleep in the past 7 days and the PROMIS eight item Sleep-Related Impairment Scale (wake disturbance) measures: level of waking alertness, sleepiness, and function in the context of sleep-wake over the past 7 days were also	Scores for fatigue, sleep disturbance and wake disturbance decreased over 12 months in the intervention groups but not the usual care control group. The fatigue score difference in the intervention groups after 12 months post-treatment, did not meet the MCID of 3 points and the difference at 12 months was not statistically significant. The sleep score reduced by 2 points at 12 months post-treatment but this was not sufficient to indicate a MCID and also was not a statistically significant result. The wake score improved by more than 4 points which suggests an MCID but again inferential statistics did not demonstrate a significance level of 0.5. .	**+** Acceptable The sample size fell significantly below that of the target e.g. 75 for each of the 3 arms was instead (n=35, n=37 and n=28). The study was, thus, underpowered The participants were from one small geographic area of the USA with the mean age being 60 and the mean severity of stroke rated on the NIHSS as mild, thus narrow data set. The clinical assessors were blinded but not the participants who were trusted not to inform the clinical assessors as to their treatment arm. This was a secondary analysis of symptoms which were not the primary target of treatment. Improvement in depression may have influenced fatigue/sleep/wake scores or vice versa. Across the 3 arms: 11%, 11% and 14% attrition rate, but no intention to treat analysis

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			Randomisation was adaptive with balance achieved on; age, gender, severity of stroke and severity of depression.	measured at entry, 8 weeks, 21 weeks and 12 months post-treatment. Estimated MCID using 0.5 standard deviation for the T score. (c) Hamilton Rating Scale for Depression (HRSD) (17 item) measured at entry, 8 weeks, 21 weeks and 12 months post-treatment. Correlational analysis among the T scores for fatigue/sleep/wake disturbance and HRSD total scores for all 4 time points were conducted		
770	E. Byun et al (2021). Brief Psychosocial Intervention to Address Poststroke Depression May Also Benefit Fatigue and Sleep-Wake Disturbance. Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses. 46: 4. 222-231.	Setting: community dwelling stroke survivors Design: Screened with demographics, NIHSS and GDS along with 2 item fatigue screening assessment. Randomisation: Use of algorithm to reduce imbalance in groups. Participants aware of which study arm but not outcome assessor Subjects: 414 patients screened, 133 met inc criteria, 100 consented. Total n=100	6 week 1 hour psychosocial-behavioural intervention by telephone or in person V usual care (inc booklet re: stroke and depression)	17 item Hamilton Rating Scale for Depression PROMIS seven item scale for fatigue PROMIS eight-item sleep scale PROMIS eight item wake scale All above carried out at entry, 8 weeks, 21 weeks and 12 months	Usual care group continued at same level of fatigue throughout the year follow-up Intervention groups had a decrease in fatigue but did not achieve MCID of 3 points by 12 months post treatment Intervention group reduced at median level by nearly 3 points (2.7), however difference at 12 months did not reach a .05 level of significance with conventional inferential statistics. Sleep disturbance decreased in intervention groups by but	**+** Acceptable Fatigue, sleep disturbance and wake disturbance decreased over the 12 month period in the intervention group but not the control group. 'This difference was clinically meaningful for wake disturbance and approached the clinically important difference for fatigue' (Abstract) 'Reduction in wake disturbance was consistent with clinically meaningful difference

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		n=37 (telephone group) n=35 (in person group) n=28 (usual care group) Inclusion: 21+yo, hospitalised with ischemic or haemorrhagic stroke within past 4 months, clinical depression symptoms. Exclusion: psychiatric co-morbidity, suicidal ideation, substance abuse, non consent, terminal illness, physical inaccessibility i.e. homelessness, aphasia, GCS <15, participation in competing research (assessed on individual basis)			remained constant in the usual group Wake disturbance improved by more than 4 points in intervention groups suggesting a MCID and worsened in the usual care group Possible that findings reflect the reduction in overall depression found in the original study. T scores showed only modest correlations at any point beyond entry date - data not show in article	standards for patient-reported outcomes, warranting further research in larger samples' (Abstract)
772	A. M. Palsdottir et al (2020). The nature stroke study; NASTRU: A randomized controlled trial of nature-based post-stroke fatigue rehabilitation. Journal of rehabilitation medicine. 52: 2.	Setting: Rehabilitation garden in Sweden. Design: 2-arm RCT to determine whether Nature-Based Rehabilitation (NBR), as add-on to standard care, has a long-term effect on post-stroke fatigue, perceived value of everyday occupations, disability, health-related quality of life (HRQoL), anxiety and depression compared with standard care alone, in people with stroke (3 months or ≥1 year post stroke). Participants: N=101 (Intervention group N=51, Control group N=50)	NBR programme was grounded in horticultural therapy. Aim: to facilitate rest and mental recovery in an enriched garden environment together with garden and horticultural occupations. NBR Content: Same structure each day, with 4 themed sessions: (*i*) morning gathering; (*ii*) physical activities (outdoors/ indoors), e.g. a garden walk,	Measures and time points: Primary: - Mental Fatigue Scale (MFS; higher scores mean more severe symptoms) and - perceived value of everyday occupations, measured as the total scores for each dimension of Occupational value instrument with pre-defined items (Oval-pd), at 8 months after randomization. Secondary: - MFS and	Target recruitment: no target as data for sample size estimation unknown. Recruitment: N=51 randomised to the intervention (NBR) group (37 sub-acute phase, 14 chronic phase); N=50 randomised to the control group (36 sub-acute phase, 14 chronic phase). Results related to fatigue only: Both NBR and Standard care group improved significantly between baseline and 8 months (trend only between baseline and 14 months).	**+** Acceptable Main limitations: - Study probably underpowered - Population mostly mild-moderate stroke severity - Time post stroke for the chronic population not reported. - Standard care not described for either group, which could have confounded findings - No intention-to-treat analysis (despite stated; analysis only based on

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		Inclusion criteria: participants in the sub-acute phase after stroke (3 months) and those in the chronic phase (at least 1 year) after stroke, aged 50–80 years, admitted to Hospital at the acute stroke stage; living in / near Malmö; independent in personal activities of daily living (ADL), reporting PSF affecting their daily lives. Exclusion criteria: dementia; severe aphasia; not fluent in Swedish; and/or with severe comorbidities.	tricycling, "on the spot" exercises; (*iii*) garden and horticultural occupation, in a group or alone, or "just being"; (*iv*) gathering for "closure for the day", with the opportunity to reflect. NBR Dose: 2 days a week, 3.5 h. per session, ≥8 weeks. Intervention was managed by the OT and horticulturalist, with input from a psychotherapist and physiotherapist. Standard care: highly individualized, depending on patients' needs and characteristics.	- Oval-pd at 14 months after randomization; - disability (modified Rankin Scale; mRS) and - anxiety and depression (Hospital Anxiety and Depression Scale; HAD) and - HRQoL (EQ-5D 3L) at 8 and 14 months after randomisation. Measured by: blinded assessor.	No statistically significant between-group difference in MFS at any point in time (P=0.91 at 8 months, P=0.80 at 14 months).	participants with outcome data)
772	A. M. Palsdottir et al (2020). The nature stroke study; NASTRU: A randomized controlled trial of nature-based post-stroke fatigue rehabilitation.	Setting: Nature based rehabilitation facility in Sweden. Design: Randomised Controlled Trial. Subjects: Stroke survivors at least 3 months post stroke who had their acute care at 1 particular	Intervention group: Within 2 weeks post randomization, participants attended a 10-week programme in groups of up to 8 participants attending a nature-based rehab (NBR) garden facility.	Post stroke fatigue as measured by the Mental Fatigue Scale (MFS). A score of >10 indicates mental fatigue. MFS measured for each participant at 8 months	Number of participants included in analysis 92/101 at 8 month follow up and 89/101 at the 14 month follow up. 4 participants died (2 in each group) before 8 month follow up. 1 person dropped out in the intervention group before 8 months. 3 dropped out in	- Low quality Poor study design, participants were not blinded, control group were not offered NBR intervention at a later date, may have accounted for high

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	Journal of rehabilitation medicine. 52: 2.	hospital and still resided in the region of the study setting. Inclusion criteria: aged 50-80, at least 3 months post stroke, independent with ADLs and experiencing post stroke fatigue. Exclusion criteria: dementia, severe aphasia and severe comorbidities.	Participants spent 3.5 hours at the NBR facility on 2 days per week. Structure of each session: morning gathering with herbal tea, physical activity session, time to 'just be' in the garden or to participate in gardening or horticultural occupations either in a group or solitary, and then a day closure gathering with refreshments. Activities were mostly outdoor (indoor if raining). Intervention was considered completed for each participant if they attended for at least 8 weeks. Attendance of 5 weeks or less was considered non-intervention. NBR was in addition to any standard care this group received post stroke. Control group: received standard care only. Standard care considered as: Individualised based	and at 14 months after randomization.	the control group by 8 months and 3 more control group participants dropped out before 14 months. Intention to treat analysis was used. At the 8 month follow up, mean MFS score in the intervention group was 8.90 and 11.06 in the control group. At 14 months, mean MFS score were 9.67 and 11.47 respectively. All of these scores were improved on the baseline measures for both groups, but there were no statistically significant differences between the groups.	drop out rate amongst this group. No power calculations, recruitment limited by funding and time allocated to study. Despite Intention to Treat analysis, results do not support any significant differences which can only be accounted for by the intervention. There is too much possibility of treatment variation in the standard care – some participants could have received no interventions, others could have been receiving multiple therapies including other fatigue management therapies. For those recruited from the group of chronic stroke survivors, they may have reached other therapy goals (partic as incl. stated independence level) and so may actually not be receiving any rehab at all in their standard care. This could account for the high dropout rate amongst control group participants. Only patients aged 50-80 independent with ADLs, without severe aphasia were included. Results cannot be generalised to the larger stroke survivor population.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
			on patient's needs at point of recovery from stroke . May have included PT, OT, SLT, psychology and mental health support. Some stroke survivors with mild deficits may not have been receiving any further rehabilitation.			The authors comment on their lower than expected recruitment rates, and how their low numbers then did not support statistical analysis. They do comment on the low drop out rate amongst intervention group participants, supporting NBR as a treatment approach with potentially high compliance amongst stroke survivors, worthy of further research but perhaps with revised methodology.
772	A. M. Palsdottir et al (2020). The nature stroke study; NASTRU: A randomized controlled trial of nature-based post-stroke fatigue rehabilitation. Journal of rehabilitation medicine. 52: 2.	All (137 – 102 chronic phase, 35 sub-acute phase)) stroke survivor participants were residents in Malmo, the third largest city in Sweden. Study design was a single blinded, 2-arm randomised control trial. Participants in the intervention arm (51 patients) were based at Alnarp Rehabilitation Garden whilst taking part in the study sessions. In the control arm (50 patients), standard care was carried out but the paper did not provide detail on setting,	A 10-week natured based rehabilitation programme in groups of 8. The programme was grounded in horticultural therapy, supported by a multimodal rehabilitation team who provided multi-sensory stimulation for physical, emotional and cognitive stimulation. 2 sessions were held per week lasting around 3.5 hours. The aim of the intervention was to facilitate mental recovery and rest.	Primary measures pre intervention and 8 months after. -Post-stroke fatigue measured with Mental Fatigue Scale (MFS). - Perceived value of everyday occupations measured with the Occupational Value Instrument with pre-defined items (Oval-pd). - These were measured again at 14 months and were considered secondary measures alongside Modified Rankin Scale, Hospital Anxiety and Depression Scale, HRQoL	Approximately a quarter of the screened patients were eligible and half of those participated. The patients with sub-acute stroke had high compliance. Participants improved, but no significant differences were found. Participants in the intervention arms fatigue score on the Mental Fatigue Scale decreased to a value below the suggested cut off for mental fatigue. No significant differences were found for either arm across all outcome measures. No significant changes were found at any time point compared to the last.	**+** This study cannot clearly state that any changes in score were because of the intervention as standard care continued for both arms and was not standardised. Also, there was a high drop out rate (20%) with many giving the reason of the long drive to and from the garden fatiguing them. As there were no significant changes, nature based therapy cannot be recommended following stroke.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
773	Y. Su et al (2020). Non-pharmacological interventions for post-stroke fatigue: Systematic review and network meta-analysis. Journal of Clinical Medicine. 9: 3. 621.	Setting: Australia, the Netherlands, China Design: systematic review network meta-analysis of RCTs: pair-wise meta-analyses with a random effects model to synthesise studies comparing intervention with control. Participants: any participants diagnosed with ischemic or hemorrhagic stroke, diagnosed by MRI or CT median age: range 47 to 69 years, disease duration: rang 2 weeks to 27 months.	Intervention group defined as providing additional non-pharmacological interventions based on usual treatment. Types identified: - Community Health Management (CHM, 1 study) - Traditional Chinese Medicine (TCM, 3 studies) - Cognitive Behavioral Therapy (CBT, 2 studies) - Respiratory Therapy (RT) and Music Therapy (MT), 2 studies - Circuit Training (CT, one study) - Hyperbaric Oxygen Therapy (HOT, one study) Control group: treatment 'as usual', including usual treatment, nursing, and rehabilitation.	Fatigue Severity Scale (FSS)	Population: 777 participants Compared with usual care, the non-pharmacological interventions resulted in a statistically significant reduction in fatigue (MD -1.46, 95% CI -1.58 to -1.35, P<0.001), but heterogeneity was high (I^2=95%). Network meta-analysis did not find any statistically significant differences between the non-pharmacological interventions.	Acceptable quality However, small body of evidence and despite being acknowledged by the authors, methodological limitations were not sufficiently taken into consideration when analysing the findings. Studies were at unclear or high risk of bias: - 8/10 had unclear allocation concealment, - 1/10 studies was at high risk and 8/10 studies were at unclear risk of performance bias (i.e. blinding of participants and staff), - 6/10 studies were at unclear risk of detection bias (i.e. assessor blinding). - 5/10 studies were at high risk of attrition bias (i.e. incomplete outcome data) - 8/10 studies were also at unclear risk of other bias. Main limitations: - No sensitivity analysis was undertaken, despite high heterogeneity - only the FSS was included. RCTs that did not have a usual care control group could not be included.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
774	Ablewhite, J., Nouri, F., Whisker, A., Thomas, S., Jones, F., das Nair, R., et al. (2022). How do stroke survivors and their caregivers manage post-stroke fatigue? A qualitative study. Clinical rehabilitation, 36(10), 1400-1410.	Setting: Community based telephone interviews Design: Semi-structured interview study. Subjects: Purposive sample of 20 stroke survivors with current or previous post-stroke fatigue. 8 care-givers who provided informal care or support.	Semi-structured telephone interviews using two interview guides (stroke survivor and carers) developed using a scoping review, research investigating post-stroke fatigue experiences and input from the research study team & patient and public involvement and engagement members. Interviews lasted between 20 and 48 minutes.	Framework analysis carried out by the research team + a PPI member to create codes and then themes from the semi-structured telephone data interviews.	Ten themes were created: acceptance of having fatigue, pacing, fatigue diaries, talking to and educating others on post-stroke fatigue, relaxation, accessing professional support, predicting situations where fatigue may happen, resting, goal setting to manage fatigue, change of diet and exercise. It was clear that management strategies varied significantly meaning a better approach instead of standardising, would be to individualise programmes as able.	**+** Acceptable -Purposive sampling allowed the findings to be more generalisable however the recruitment strategy (online and social media platforms) likely contributed to the young and not quite so generalisable age bracket of participants. Also all care-givers were partners which reduces generalisability. Wonder if any participants living alone without close friends/family were included and if there were differences in findings within this sample. -Strong interview guide development in terms of groups involved and pilot study prior. -No outcome measure/professional reviewing re inclusion criteria having PSF. -Did the PPIE member doing coding have previous experience as it reads that the research team did not code them -? Adequate presentation of results often showing one view point for both stroke survivor and care giver but starting with 'some'.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
774	Ablewhite, J., Nouri, F., Whisker, A., Thomas, S., Jones, F., das Nair, R., et al. (2022). How do stroke survivors and their caregivers manage post-stroke fatigue? A qualitative study. Clinical rehabilitation, 36(10), 1400-1410.	Setting: community Design: Qualitative, descriptive study to gain insight into the lived experiences of using day-to-day strategies to manage post-stroke fatigue. Participants: 20 stroke survivors with current, or previous, post-stroke fatigue, and 8 care-givers, who provided informal care or support	Day-to-day strategies to manage post-stroke fatigue	N/A	People with stroke rarely receive information or advice from HCPs on how to manage PSF. Professional support is often found to be helpful. Strategies found to be helpful by some (not all): ● Learning to accept PSF ● Pacing ● Using an activity diary ● Relaxation ● Resting ● Goal setting and graded activity ● Seeking support from professionals and peers ● Educating family and friends about PSF Caregivers played an important role in overseeing the implementation of strategies to manage fatigue.	N/A Main limitations: COVID-19 limited opportunities to involve people with severe communication or cognitive problems by preventing in-person face-to-face interviews. COVID-19 resulted in a reliance on recruiting people remotely. More participants were under 50 years of age, probably due to use of social media. Participants self-defined their fatigue. Some of the participants were several years after their stroke, and their fatigue may also have been due to new additional factors.
771	Drummond et al. (2021). Managing post-stroke fatigue: A qualitative study to explore multifaceted clinical perspectives. British Journal of Occupational Therapy : 3.080226211e+15	Setting: UK with 2 participants out with UK (Australia and Europe) Design: Qualitative semi-structured interview via video link or telephone call. Participants: 20 participants 9 OTs; 5 PTs; 3 RNs; 3 Psychologists Various backgrounds, some health, some academia and some private care.	Semi-structured interview to determine clinician's views of post stroke fatigue management. As well as demographics and conditions treated, the questionnaire covered key issues patients present with; use of any fatigue Ax; how current evidence affected practice; opinion on key	'Key Findings • Clinicians rely on their own knowledge to manage fatigue (10) • There are clear overlaps in post-stroke and 'other' fatigue management (10). • OTs view fatigue management as a core area of practice. (10) What the study has added. Clinicians rely heavily on their own knowledge and the	Participants acknowledge fatigue management as important but with limited research, primarily relied on their own clinical knowledge and experience. Assessment of fatigue often based on subjective methods including patient history Similar strategies adopted by participants but some difference in how techniques are used	**N/A**

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			elements of fatigue management programme	strategies employed for managing patients with fatigue, across different conditions, are similar. Clinicians recognise the need for underpinning research.'	Common themes: assessment (subjective); use of strategies (pacing, diaries, etc); education (inc family) Seen as a long-term intervention suggesting more appropriate within primary care/community services and general consensus of self-management approach for long-term benefit	
771	Drummond et al. (2021). Managing post-stroke fatigue: A qualitative study to explore multifaceted clinical perspectives. British Journal of Occupational Therapy : 3.080226211e+15	Setting: different settings Design Qualitative interview study to gain insights into the experiences of clinicians who routinely manage patients with fatigue. Framework approach. Participants: N=20 (9 OTs, 5 PTs, 3 nurses, 3 psychologists from UK and abroad).	N/A	N/A	Fatigue management strategies mainly informed by participants' own knowledge. Common strategies included: Diaries, Pacing and prioritising techniques, Fatigue education for stroke survivor and family, Adoption of coping strategies (incl. compensatory techniques and equipment or environment modification); Exercise; Development of fatigue management: many felt this should be flexible to meet individual needs, developed with service users, and be available long term. PSF assessment: lack of use of validated tools and routine assessment of PSF.	**N/A** Strength: included views of experienced HCPs Limitations: no response from doctors Possibly response bias from self-selected study population.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
775	Ablewhite et al. (2022). UK clinical approaches to address post-stroke fatigue: findings from The Nottingham Fatigue after Stroke study. International Journal of Therapy and Rehabilitation 29:5 44896	Design: A cross-sectional survey Participants and Setting Allied health professionals, psychologists, doctors and nurses working clinically in hospitals, the community or both, who routinely provided information, management or treatment to people with PSF.	N/A	N/A	305 questionnaires analysed; majority from OTs (56%, *n*=171). Post-stroke management included pacing (67%, *n*=204), fatigue diary (39%, *n*=119), education (38%, *n*=117). Marked variations in type, amount and length of support and follow up; not primarily based on need. Variable levels of confidence in PSF management. Lack of standardised assessment of PSF.	**N/A** Strength: UK-wide survey from a range of HCPs. Limitations: response rate unknown. Possible response bias (self-selecting sample). Heterogeneity in service data made it difficult to pool information.
776	Hinkle et al. (2017). Poststroke Fatigue: Emerging Evidence and Approaches to Management: A Scientific Statement for Healthcare Professionals from the American Heart Association. Stroke 48:7 e159-e170	Design: Scientific statement including a critical analysis of quantitative research and guidelines on PSF.	Pharmacological interventions Non- pharmacological interventions	Fatigue	The Cochrane systematic review included in this statement has been superseded by later publications. All other studies included in this statement are not eligible for this guideline update due to their publication date, design, and/ or exploratory nature.	- Quality appraisal of the critical analysis of quantitative research only: Low quality review Main limitations: Limited reporting of the search strategy, unclear information on independent study selection and data extraction, no evidence tables for intervention studies, lack of clarity on quality appraisal method.
738	Lanctot et al. (2020). Canadian Stroke Best Practice Recommendations: Mood, Cognition and Fatigue following	2019 update of the Canadian Stroke Best Practice Recommendations (CSBPR) for Mood, Cognition and Fatigue following Stroke.	Pharmacological and non-pharmacological interventions. Pharmacological: selective serotonin reuptake inhibitors	Fatigue outcomes reported include: -Post Stroke Fatigue (PSF) prevalence -Fatigue Severity Scale (FSS) and FSS-7	Cochrane review (Wu S et al., 2015 Interventions for post-stroke fatigue) from seven trials (five pharmacological, two non-pharmacological), found that	(+) acceptable given the source and explicit detail of the evidence underpinning recommendations made. Further analysis of the quality of each trial may be required.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Stroke, 6th edition update 2019. International Journal of Stroke 15:6 668-688	Details of the underpinning systematic review process to inform the recommendations are not provided. Subjects: Stroke or TIA	(fluoxetine) and modafinil Non-pharmacological: -Group cognitive treatment (f cognitive behavioral therapy and compensatory strategy teaching) +/- combined with graded activity training (COGRAT) -Mindfulness-based stress reduction -Fatigue management education program -Chronic disease self-management program.	-Multidimensional Fatigue Inventory (MFI)-20 -Epworth Sleepiness Scale	overall, treatment resulted in a significant reduction in fatigue scores (weighted mean difference (WMD)= -1.07, 95% CI 1.93, 0.21, p= 0.014). Pharmacological only: One positive RCT: MIDAS trial (Bivard A et al., 2017), N= 36 Active treatment with modafinil 200 mg vs placebo decreased MFI-20 scores (MD= 7.38, 95% CI 21.76 to 2.99; p < 0.001), and FSS scores (MD= 6.31, 95% CI 10.7 to 1.9, p= 0.048). Two negative trials: Poulsen et al 2015 RCT, N=41 400 mg modafinil for 90 days vs placebo. median MFI-20 GF score (11 modafinil vs. placebo 14, p = 0.32), or in the median score of other MFI domains (physical fatigue, reduced activity, reduced motivation); however median FSS and FSS-7 were significantly lower at 90 days (36 vs. 49.5, p= 0.02 and 22 vs. 37.5, p= 0.042). Choi-Kwon S et al 2007. N=83 Fluoxetine 20 mg/day vs placebo for three months. No significant differences in the number of patients with PSF. At six months, 34 patients (85%) in the fluoxetine group reported PSF compared with 40 (93%) in the control group.	References one Cochrane review with meta-analysis of mixed interventions (pharmacological/ non-pharmacological studies) details a number of relatively small RCTs often with conflicting findings

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					Non-pharmacological Interventions Two positive RCTs Zedlitz et al., 2012; N=83 with severe fatigue >4 months post stroke; 12-week program. Cognitive treatment combined with graded activity training (COGRAT) group vs cognitive treatment (control condition had clinically relevant improvement in fatigue severity (57.9% vs. 24.4%, p=0.002). Johansson et al., 2012 N=18 stroke and TBI participants in eight-week program of mindfulness-based stress reduction vs wait list control had a significantly greater decrease in Mental Fatigue Scale scores compared to a wait list control group. Negative RCT Clarke A et al., 2012 N=19 tested a fatigue management education program vs stroke education programme with no between group difference in FSS Longitudinal follow-up of a RCT Lorig KR et al 2001; N=831 with heart disease, lung disease, stroke, or arthritis showed no difference in fatigue outcomes when compared to baseline at 1 year and 2 year follow-up	

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
738	LanctÔt et al. (2020). Canadian Stroke Best Practice Recommendations: Mood, Cognition and Fatigue following Stroke, 6th edition update 2019. International Journal of Stroke 15:6 668-688	Design: best practice recommendations, using a framework adapted from the Practice Guideline Evaluation and Adaptation Cycle, including a systematic literature search.	Pharmacological interventions Non- pharmacological interventions	Fatigue	The Cochrane systematic review included in this statement has been superseded by later publications. All other studies included in these recommendations are not eligible for this guideline update due to their publication date, design, and/ or exploratory nature.	+ Quality appraisal of the systematic search: Acceptable quality review A comprehensive, systematic search was undertaken and evidence tables were provided. Levels of evidence were indicated. Main limitations: Unclear information on independent study selection and data extraction, some lack of clarity on quality appraisal method.

Post-stroke fatigue definitions

People with stroke describe post-stroke fatigue as ‘a fatigue like no other’ (Thomas et al., 2019a), which may not be ameliorated by rest (Worthington et al., 2017). Post-stroke fatigue has been described in different ways but there is no consensus on its definition (Hinkle et al., 2017). The following case definitions for post-stroke fatigue have demonstrated concurrent validity, reliability and feasibility in clinical practice (Lynch et al., 2007, p. 543):

- For people with stroke in hospital: ‘Since their stroke, the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities (for inpatients this may include therapy and may include the need to terminate an activity early because of fatigue).’
- For people with stroke in the community: ‘Over the past month, there has been at least a 2-week period when patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities’.