CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

MOOD, COGNITION AND FATIGUE FOLLOWING STROKE EVIDENCE TABLES

Post-Stroke Depression: Pharmacotherapy and Combined Treatment

Update 2019

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

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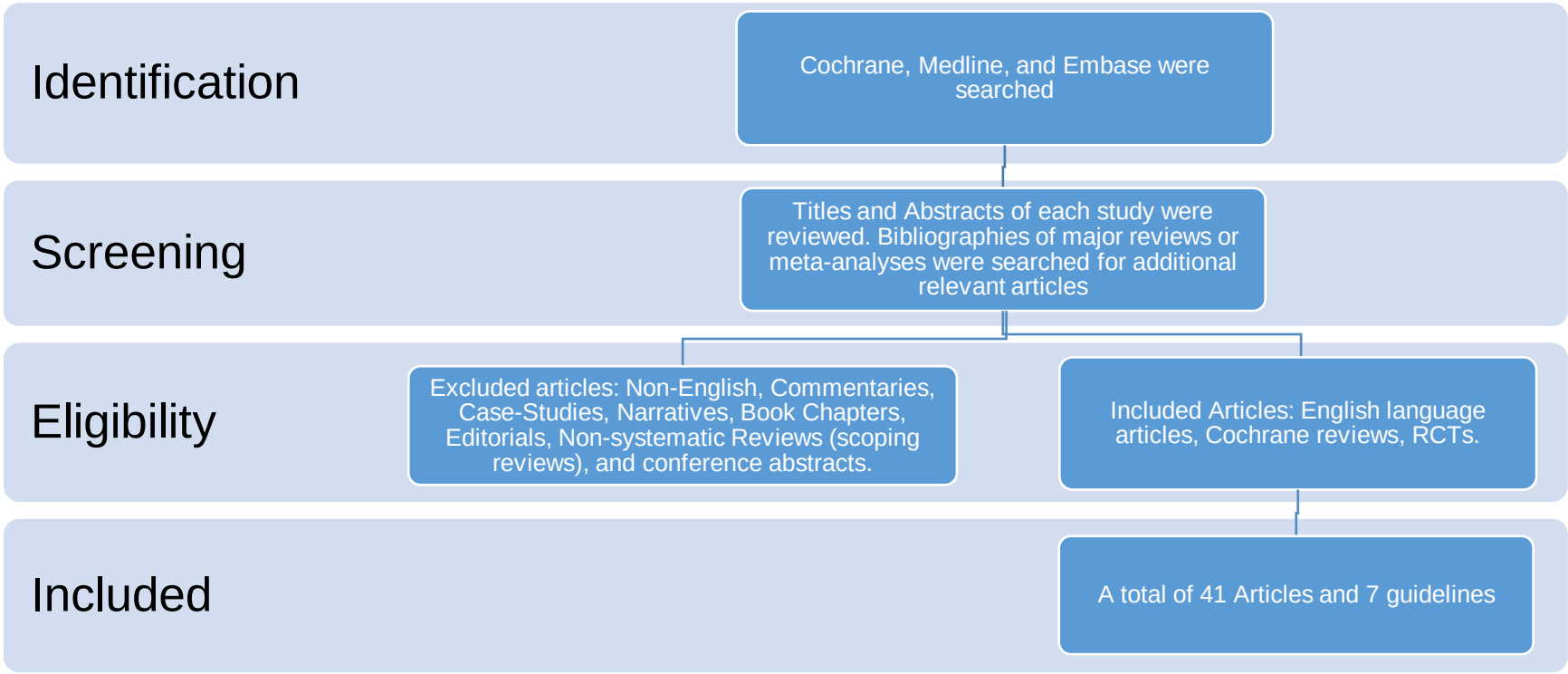
Search Strategy



The Medline, Embase, PsycInfo, and Cochrane databases were searched using the terms [stroke OR cerebrovascular disorders] and [depression OR depressive disorders OR anxiety OR anxiety disorders OR emotional incontinence]. The title and abstract of each article was reviewed for relevance. 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 41 articles and 7 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110**	4.9.2. Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness. Class I; LOE B-R
Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. (Part 6)	Strong recommendation Updated For stroke survivors with depression or depressive symptoms, antidepressants, which includes SSRIs should be considered. There is no clear evidence that particular antidepressants produce greater effects than others and will vary according to the benefit and risk profile of the individual.
Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela **BM, Mitchell PH, Skolarus LE, Whooley MA, Williams LS; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research.** **Poststroke depression: a scientific statement for healthcare professionals from the** **American Heart Association/American Stroke Association.** ***Stroke* 2016;48(2):e30-e43**	**Summary of Findings** Twelve trials (n=1121) suggest that antidepressant medications may be effective in treating PSD; further research is needed to determine optimal timing, threshold, and medications for treatment**.**
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. **Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.**	Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness. Class I; LOE B. A therapeutic trial of an SSRI or dextromethorphan/quinidine is reasonable for patients with emotional lability or pseudobulbar affect causing emotional distress. Class IIa; LOE A Combining pharmacological and nonpharmacological treatments of poststroke depression may be considered. Class IIb; LOE A. No recommendation for the use of any particular class of antidepressants is made. SSRIs are commonly used and generally well tolerated in this patient population. Class III;LOE A.

Guideline	Recommendations
***Stroke* 2016;47:e98–e169.** **(selected)**	
Intercollegiate Stroke Working Party. National clinical guideline for stroke, *5th* edition. London: Royal College of Physicians, 2016	**Anxiety, depression and psychological distress** A People with stroke with one mood disorder (e.g. depression) should be assessed for others (e.g. anxiety). E People with depression or anxiety after stroke who are treated with antidepressant medication should be monitored for adverse effects and treated for at least four months beyond initial recovery. If the person's mood has not improved after 2-4 weeks, medication adherence should be checked before considering a dose increase or a change to another antidepressant. F People with severe or persistent symptoms of emotional disturbance after stroke should receive specialist assessment and treatment from a clinical neuropsychologist/clinical psychologist. G People with persistent moderate to severe emotional disturbance after stroke who have not responded to high intensity psychological intervention or pharmacological treatment should be considered for collaborative care. Their care should involve collaboration between the GP, primary and secondary physical health services and case management, with supervision from a senior mental health professional and should include long term follow-up. **Emotionalism** A. Any patient who persistently cries or laughs in unexpected situations or who is upset by their fluctuating emotional state should be assessed by a specialist or member of the stroke team trained in the assessment of emotionalism. B. Any patient diagnosed with emotionalism should, when they show increased emotional behaviour, be appropriately distracted from the provoking stimuli. C. Patients with severe, persistent or troublesome emotionalism should be given antidepressant drug treatment, monitoring the frequency of crying to check effectiveness. Patients should be monitored for known adverse effects. If the emotionalism has not improved 2–4 weeks after initiating treatment, check that the patient is taking the medicine as prescribed. If they are, then consider increasing the dose or changing to another antidepressant.
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning: A national clinical guideline, 2010. Edinburgh, Scotland.	**Preventing post-stroke depression** 1. Routine prescription of antidepressants is not recommended to prevent post-stroke depression (B). 2. Offering routine psychological therapies in one-to-one format following a stroke is not recommended to prevent post-stroke depression (B). 3. Psychological principles from motivational interviewing and problem solving should be incorporated into education programmes for people who have had a stroke (B). 4. Stroke rehabilitation services should consider structured, psychologically-based programmes (incorporating education and advice) to target individuals' emotional adjustment to the impact of stroke, and to increase their sense of control over their recovery. Such programmes require staff training and ongoing evaluation to ensure clinical benefit (GPP). **Treating post-stroke depression** 1. Patients with post-stroke depression should be considered for antidepressant treatment, with decisions made on an individual basis. Clinicians should monitor response to treatment, plan regular reviews and should be vigilant to the possible occurrence of unwanted side effects, issues of adherence to medication and the possibility of symptom relapse (A). 2. Clinicians need to make decisions on the choice of antidepressant on a case-by-case basis, taking into account factors such as risk of seizures, falls and delirium (GPP). 3. Patients who fail to respond to antidepressant therapy, or who do not wish to take medication, should be considered for a trial of talking-based therapy, with clinicians carefully monitoring response to treatment (GPP).

Guideline	Recommendations
	4. Clinicians should be aware that environmental factors (eg opportunities for social interaction, noise levels) often have an impact on mood, and should consider whether it is possible to alter these factors when individuals experience post-stroke depression (GPP). **Emotional lability** 1. Patients with post-stroke emotionalism may be considered for a course of antidepressant medication (B). 2. Possible side effects of antidepressant treatment should be explained to patients prior to commencing treatment (GPP). 3. Patients and carers should be offered a clear explanation and advice about emotionalism, and considered for psychological (talking-based) support if they have a poor response to antidepressant medication and show evidence of distress about their condition. Local psychological support, education and advice should be considered on an individual basis as available. Such advice should be embedded in general education programmes. **Post-stroke emotional adjustment** 1. People who have had a stroke should be considered for workbook approaches that aim to address their beliefs and attitudes about their recovery (GPP). **Summary of Recommendations** 1. Appropriate referral to health and clinical psychology services should be considered for patients and carers to promote good recovery/adaptation and prevent and treat abnormal adaptation to the consequences of stroke (GPP). 2. All stroke patients (including those cared for in primary care) should be screened for mood disturbance (GPP). 3. Some form of screening should occur, eg using the Stroke Aphasic Depression Questionnaire (SAD-Q) or General Health Questionnaire of 12 items (GHQ-12): • as early as appropriate and definitely before discharge, and • at regular intervals thereafter 4. Clinical judgement should be used to determine how regularly mood should be re-assessed (GPP). If an individual is suspected of having a mood disorder they should be referred to an appropriately trained professional for a full assessment, or to a rehabilitation team member who has received training in the identification of psychological distress (GPP).
VA/DoD clinical practice guideline for the management of stroke rehabilitation 2010.	**Post stroke depression** 1. There are several treatment options for the patient with stroke and mild depression that can be used alone or in combination based on the patient's individual need and preference for services. Refer to VA/DoD guidelines for the management of Major Depression Disorder (MDD). 2. Patients diagnosed with moderate to severe depression after stroke should be referred to Mental Health specialty for evaluation and treatment. 3. There is conflicting evidence regarding the use of routine pharmacotherapy or psychotherapy to prevent depression or other mood disorders following stroke. 4. Patients with stroke who are suspected of wishing to harm themselves or others (suicidal or homicidal ideation) should be referred immediately to Mental Health for evaluation. 5. Recommend that patients with stroke should be given information, advice, and the opportunity to talk about the impact of the illness upon their lives. **Other Mood Disorders** 6. Patients following stroke exhibiting extreme emotional lability (i.e. pathological crying/tearfulness) should be given a trial of antidepressant medication, if no contraindication exists. SSRIs are recommended in this patient population. [A] 7. Patients with stroke who are diagnosed with anxiety related disorders should be evaluated for pharmacotherapy options. Consider psychotherapy intervention for anxiety and panic. Cognitive Behavioral Therapy has been found to be a more efficacious treatment for anxiety and panic disorder than other therapeutic interventions. 8. Recommend skills training regarding Activities of Daily Living (ADL's), and psychoeducation regarding stroke recovery with the family.

Guideline	Recommendations
	9. Encourage the patient with stroke to become involved in physical and/or other leisure activities. **Assessment of emotional and behavioral state** 1. Initial evaluation of the patient should include a psychosocial history that covers pre-morbid personality characteristics, psychological disorders, pre-morbid social roles, and level of available social support. 2. Brief, continual assessments of psychological adjustment should be conducted to quickly identify when new problems occur. These assessments should also include ongoing monitoring of suicidal ideation and substance abuse. Other psychological factors deserving attention include: level of insight, level of self-efficacy/locus of control, loss of identity concerns, social support, sexuality, and sleep. 3. Review all medications and supplements including over the counter (OTC) medications that may affect behavior and function. 4. Inclusion of collateral information (e.g., spouse, children) is recommended to obtain a comprehensive picture of the patient's pre-morbid functioning and psychological changes since the stroke. 5. There is insufficient evidence to recommend the use of any specific tools to assess psychological adjustment. Several screening and assessment tools exist. (See Appendix B for standard instruments for psychological assessment.) 6. Post-stroke patients should be assessed for other psychiatric illnesses, including anxiety, bipolar illness, SUD, and nicotine dependence. Refer for further evaluation by mental health if indicated. **Use of standardized assessments** 1. Recommend that all patients should be screened for depression and motor, sensory, cognitive, communication, and swallowing deficits by appropriately trained clinicians, using standardized and valid screening tools. [C] If depression, or motor, sensory, cognitive, communication, or swallowing deficits are found on initial screening assessment, patients should be formally assessed by the appropriate clinician from the coordinated rehabilitation team. [C]

Evidence Tables

Pharmacotherapy for the Treatment of Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Meta-analyses					
Xu et al. 2016 **China** **Systematic review & meta-analysis**	NA	11 RCTs (n=740) including patients with a clinical diagnosis of post-stroke depression (PSD). Sample sizes ranged from 17-229. Mean age was 67.1 years, 47.6% were female. Criteria to establish depression included DSM III or IV (n=5), Hamilton Depression Scale score>15 (n=1), DSM +depression scale score>cut off (n=2), ICD-10 (n=1), other (n=1) and not reported (n=1)	Trials compared treatment with an antidepressant(s) vs. placebo. Mean duration of treatment was 10 weeks. Agents included SSRIs (n=7), TCAs (n=3) and other (n=2). Two trials compared 2 agents with placebo.	**Primary outcome:** Mean change in depression score from baseline **Secondary outcome:** Treatment response	Treatment with an antidepressant was associated with a significant reduction in depression scores (SMD=-0.96, 95% CI -1.41 to -0.51, p<0.0001). Response to treatment was significantly higher with active treatment (RR=1.36, 95% CI 1.01-1.83, p=0.04). In sub group analyses, younger age (<70 years) and female sex were associated with significantly better response to treatment (i.e. greater reductions in depression scale scores). Persons receiving active treatment were significantly more likely to withdraw from studies due to adverse events (RR=2.72, 95% CI 1.37-5.43, p=0.004).
Hackett et al. 2008 **Australia** **Cochrane Review**	NA	12 RCTs (n=1,121), including patients following stroke with a diagnosis of 1) depressive disorder, as defined by symptom scores on a standard screening instrument; (2 major depression, and 3) dysthymia or minor depression.	Trials compared SSRIs vs placebo (n=7), tricyclic antidepressants vs. placebo (n=2), and other agents vs. placebo (n=4). Treatment duration ranged from 4-26 weeks. 4 additional trials in this review examined treatment with electroconvulsive treatment (ECT) and psychotherapy.	**Primary outcome:** Prevalence of diagnosable depressive disorder following treatment. **Secondary outcomes:** Depression rating scale scores, physical function, and mortality.	The time from stroke onset to study entry ranged from a few days to 25 months. Pharmacotherapy was associated with a small, but significant, positive treatment effect in terms of treating depression (pooled OR = 0.47; 95% CI 0.22-0.98) and reducing depressive symptomatology (pooled OR = 0.22 (95% CI 0.09-0.52). Many adverse events were reported.
Chen et al. 2006 **USA** **Systematic review & Meta-analysis**	NA	16 RCTs representing 1,320 stroke patients with a diagnosis of depression at baseline.	Included studies compared any single antidepressant with placebo. Trials compared SSRIs vs placebo (n=7), tricyclic antidepressants vs. placebo (n=2), and other agents vs. placebo (n=3). Treatment duration ranged from 4-26 weeks.	**Primary outcomes:** Response rate, depression rating scale scores, and improvement in ADLs or neurologic impairment.	The treatment response rate was significantly better in the active treatment group (65.18% vs. 44.37%; rate difference was 0.23, 95% CI 0.03-0.43). A relationship between duration and benefit of treatment was identified. Analysis of studies with treatment durations of 1 and 2 weeks revealed no significant treatment effects; however, from 3 weeks onward, demonstrated effects were, generally, of increasing significance. Treatment was not found to have a significant impact on improvement in ADLs or neurologic impairment.
Placebo-controlled Trials of Pharmacotherapy					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Robinson et al. 2008 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	159 patients (10 days – 3 months post stroke) with a DSM-IV diagnosis of "depression due to stroke with major depressive-like episode" and a HRSD score ≥18. Mean ages were 66.8, 64.7 and 68.1 in the placebo and 2 treatment groups, respectively. 53.5% were female. There were no significant between group differences noted at baseline.	Participants were randomly assigned to receive 1 of 3 treatments for 12 weeks: i) 600 mg nefiracetam (n=55), ii) 900 mg nefiracetam (n=48) or iii) matching placebo.	**Primary outcome:** Change in depression severity, assessed by the Hamilton Rating Scale for Depression (HRSD) at the end of treatment.	There was no significant time X treatment effect of 600 mg or 900 mg nefiracetam when compared with placebo. There were no significant effects identified on an item-by-item analysis of the HRSD. A *post hoc* analysis identified a significant effect of treatment among the most severely depressed quintile of patients treated with 900 mg nefiracetam compared with placebo (p=0.05). Among participants who had completed at least 4 weeks of treatment (n=137), response rates (i.e. >50% decline in HRSD scores) were 76.5%, 71.8% and 71.4% for the 800 mg, 600 mg and placebo groups, respectively. Remission rates (HRSD scores of ≤8 at the end of treatment) were 41.2%, 43.6% and 40.5% for the 900, 600 mg and placebo groups, respectively. No assessment of adverse events was reported.
Choi-Kwon et al. 2006 **South Korea** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	152 stroke patients with one of post stroke depression (average of 14 months post stroke), emotional incontinence or anger proneness. Individuals with SAH, severe communication problems, scored ≤23 on MMSE, or who had a history of depression prior to stroke, were excluded. Mean age was 58 years, 77% were male.	Participants were randomly assigned to receive either treatment with fluoxetine 20 mg/day (n=76) or matching placebo (n=79) in a single morning dose for 3 months.	**Primary outcomes:** Mean score on Beck Depression Inventory (BDI) for PSD, and percentage change in VAS score for emotional incontinence and anger proneness, at 3 and 6 months.	There was complete data at 3 and 6 months follow-up for 64 patients in the placebo group and 61 patients in the fluoxetine group. A total of 32 patients in the treatment group and 19 patients in the control group were diagnosed with PSD. The severity of PSD was judged to be mild (mean BDI = 19). Over time, there was a trend identified toward a decrease in depressive symptoms in both the treatment and the control condition. Treatment with fluoxetine was not associated with a significant improvement in depression at follow-up. There were no significant between group differences reported in terms of adverse events reported. Effects reported in the fluoxetine group included nausea, headache, insomnia, GI discomfort, decreased appetite.
Murray et al. 2005 **Sweden** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	123 stroke patients identified from 4 Swedish stroke centres with either a major (n=76) or minor (n=47) depressive episode (defined according to the DSM-IV), an average of 128 days after stroke. Mean age was 71 years, 47% were male.	Participants were assigned to either the treatment or placebo conditions. 62 patients received sertraline (50 – 100 mg/day) and 61 received a matching placebo for 26 weeks.	**Primary outcome:** Change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to weeks 6 and 26. **Secondary outcomes:**	Both groups demonstrated significant improvements in depressive symptoms over time, but there were no significant differences between groups in change in MADRS scores over the treatment period. There was a significantly greater improvement in EDS score at 6 weeks, favouring treatment with sertraline (p<0.05), but not at 26 weeks.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Emotional Distress Scale (EDS), Change in perceived Quality of Life (QoL)	Improvement in perceived QoL was significantly greater for patients treated with sertraline at week 26 compared with the control group (p<0.05), but not an 6 weeks.
Rampello et al. 2005 **Italy** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	31 outpatients recruited within 12 months of ischemic or haemorrhagic stroke who also had a diagnosis of major or minor depression according to DSM-IV criteria in addition to the presence of retarded depression. Mean age was 77 years, 45% were male. Mean time since stroke was approximately 12 weeks.	Patients were randomly assigned to receive either treatment with, 4 mg, bid of reboxetine (n=16) or a matching placebo (n=15) for 16 weeks. Side effects reported by patients were recorded at each visit and patients were asked whether they remembered to take their medication regularly.	**Primary outcome:** "efficacy", defined as 1) variations in Hamilton Depression Rating Scale (HRSD) and Beck Depression Inventory (BDI) scores and 2) variations in the Synoptic Table Scores (used to distinguish retarded from anxious depression), assessed at baseline, 4, 8 and 16 weeks.	Patients in the treatment condition experienced significant improvement from baseline to 4, 8 & 16 weeks on both the HDRS and BDI (p<0.01 for all comparisons), while there was no significant change reported for patients who were assigned to receive placebo. At each assessment point, between group comparisons revealed significant reduction in HRSD scores in the group of patients assigned to treatment with reboxetine when compared to placebo (p<0.01 at 4, 8 and 16 weeks). The numbers of the most commonly reported side effects were similar between groups: dryness of feces, constipation, hyperperspiration, hypotension and sinusal tachycardia.
Fruehwald et al. 2003 **Austria** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	54 patients admitted to 2 hospitals following acute stroke, diagnosed with moderate to severe post-stroke depression Individuals with significant communication impairments or more than mild cognitive impairments were not included in the study. Mean age was 64 years, 58% were male. Mean time from stroke onset was 11 days.	Patients were randomly assigned within 2 weeks of stroke to receive treatment with either 20-40 mg fluoxetine (n=26) or matching placebo (n=24) for 12 weeks. If at the 4-week evaluation, the participant did not demonstrate response (ie. HDS >13), treatment was continued at a doubled dose, for an additional 8 weeks.	**Primary outcome:** Average change in Hamilton Depression Scale (HDS) score 4 weeks after treatment **Secondary outcomes:** Average changes in HDS at 3 months and at long-term follow-up (18 months), the average changes in Beck Depression Inventory (BDI) and the number of responders (patients with an HDS < 13).	Both groups demonstrated significant within group improvement over 4 weeks, but the difference between groups was not significant. Mean HSD scores decreased from 32.8 to 14.7 in the fluoxetine group vs. 30.3 to 11.7 in the placebo group. At 18 months, the mean HDS and BDI scores were significantly lower in the fluoxetine group (10.8 vs. 22.2, p<0.05, and 5.3 vs. 8.5, p<0.05, respectively). The mean change in HDS scores was significantly greater in the fluoxetine group (-22.2 vs. -8.8, p<0.05). At 18 months, the percentage of responders was significantly higher in the fluoxetine group (81.8% vs. 27.8%, p<0.01). No major side effects were reported. Minor effects reported by participants included dizziness, nausea and cephalalgia.
Wiart et al. 2000 **France** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒	31 patients with a recent (within 3 months) ischemic stroke who were hemiplegic, with a diagnosis of major depressive disorder. Patients with a history of multiple strokes, severe aphasia and/or cognitive impairment were excluded. Mean age was 67 years. Mean	Participants were randomly assigned to receive treatment with either 20 mg fluoxetine (n=16) or matching placebo (n=15) for 45 days (6 weeks).	**Primary outcome:** Changes in standardized test scores at days 15, 30 and 45. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Other measures included the Motricity Index and FIM	At the end of 6 weeks, participants in the fluoxetine demonstrated greater improvement on MADRS scores (-16.6 vs. -8.4, p<0.02). Response rates were non-significantly higher in the fluoxetine group (62.5% vs. 33.3%, p=0.1).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	ITT: ☑	time since stroke onset was 47 days.			There were improvements in function demonstrated by both groups, but no significant differences between groups. Side effects reported by individuals assigned to fluoxetine included, nausea, seizure, tremor, confusion, increased transaminases.
Robinson et al. 2000 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	56 adults, aged 18-85 years recovering from stroke with onset of <6 months, diagnosed with major or minor depression (based on DSM IV criteria or Hamilton Depression Scale score <12. Mean ages ranged from 64-73 years across treatment groups. Mean time from stroke onset ranged from 5-6 weeks. 48 individuals with no diagnosis of depression were enrolled in the study in order to assess effects of antidepressant use on recovery.	Participants were randomized to receive either fluoxetine (10mg/d gradually increased to 40 mg/day, n=23) or nortriptyline (dose of 25 mg/day gradually increased to 100 mg/day, n=16) or placebo (n=17) for 12 weeks. Participants then crossed-over to 12 weeks of placebo treatment.	**Primary outcome:** Hamilton Rating Scale for Depression (HRSD-28), assessed at baseline and at each 3-week evaluation point. **Secondary outcome:** Successful response to treatment, defined as a >50% reduction in the HRSD scale score + failure to fulfill the criteria for major or minor depression.	Patients treated with nortriptyline had greater declines in HRSD scores compared with those treated with either fluoxetine or with placebo at 12 weeks follow-up, after adjustment for baseline differences in HRSD scores. The rate of successful treatment was 77% in the nortriptyline group, 14% in the fluoxetine group and 31% in the placebo condition. Neither depressed nor non-depressed patients in either active treatment condition demonstrated significant greater improvement in functional recover than those assigned to placebo. Adverse events included weight loss (fluoxetine in elderly patients), anxiety, insomnia and GI symptoms
Grade et al. 1998 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor☑ ITT: ☒	21 adults admitted to a community-based rehab unit, following stroke. Patients with severe cognitive impairment (unable to understand or comply with instruction) were excluded from participation. Mean age was 71 years, 52% were male. Mean time since stroke was 18 days	Patients were randomly assigned to treatment with either 30mg of methylphenidate (n=10) or placebo (n=11) + physical therapy for 3 weeks.	**Primary outcome:** Depression/symptoms of depression, assessed using the HRSD (25 item) and the Zung Depression Scale **Secondary outcomes:** Cognitive status, motor function and ADLs were also evaluated.	After adjustment for baseline differences in depression scores, patients in the methylphenidate group demonstrated greater improvement, scoring significantly lower on HAM-D (p=0.028) and the Zung scale (p=0.055) at the end of treatment, as well as higher on the motor-FIM (p=0.032). There were no significant differences Fugl-Meyer or MMSE scores between groups at the end of treatment. There were no significant between group differences demonstrated on the MMSE (p=0.54) or in terms of number of side effects reported (p=0.94).
Andersen et al. 1994 **Denmark** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	66 patients, aged 18-80 years, recovering from stroke with moderate depression (defined as a baseline Hamilton Depression Scale score ≥ 13 and symptom duration of at least 2 weeks), enrolled 2 to 52 weeks after stroke. Mean age was 67 years, 39% were male. Mean time from stroke onset was 12 weeks.	Patients were randomized 1:1, to receive the "recommended" dose of citalopram (20 mg for those <66 years, or 10 mg for those individuals ≥66 years) for 6 weeks. At that point, for non-responders (defined as HRSD scores > 13), participants were offered treatment with either nortriptyline or mianserin.	**Primary outcome:** Hamilton Depression Scale (HDS) and the Melancholia Scale, assessed 6 weeks after treatment **Secondary outcome:** Response rate, defined as a decrease of >50% on HDS scores	Treatment with citalopram was associated with significantly greater improvement in HDS scores over 6 weeks (mean change of -8.0 ±6.0 vs. -4.8 ±4.6, p<0.05) and on the Melancholia Scale (-7.2±5.8 vs. 4.3±4.1, p<0.05). At 6 weeks, the percentage of responders was significantly greater in the citalopram group (59% vs. 28%, p<0.05).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			For responders (HRSD scores < 13), treatment was continued for an additional 10 weeks.		At 16 weeks, the mean HDS score was significantly lower in the citalopram group (6.2±2.3 vs. 8.7±2.2, p<0.05). There number of adverse events was similar between groups.
Reding et al. 1986 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☒	27 patients with or without depression, enrolled in an inpatient stroke rehabilitation program. Among the patients recruited, unknown numbers had a clinical diagnosis of depression at baseline. Depression was identified by an abnormal Zung Depression Scale score, or an abnormal dexamethasone suppression test (DST). Mean ages across these groups ranged 63-73 years, mean days from stroke onset ranged from 24 to 51 days.	Participants were randomly assigned to receive either trazodone (200 mg daily, maximum dose, n=14) or placebo (n=13) for the duration of their rehabilitation stay.	**Primary outcome:** Improvement in Barthel Index (BI) scores, at end of treatment	The mean duration of treatment was 32 days (trazadone) and 25 days (placebo) For patients with a clinical diagnosis of depression at baseline, there was a non-significantly greater improvement in mean BI scores for patients receiving trazadone (28±7 vs. 20±7, p=n/s). Among patients with an abnormal Zung score, the mean improvement in BI scores was non-significantly greater in the trazadone group (46±5 vs. 18±9, p=n/s). Among patients with an abnormal DST, the mean improvement in BI scores was significantly greater in the trazadone group (38±6 vs. 20±6, p<0.05). The study was discontinued for 6 patients in the placebo group AND 6 patients in the trazodone group, due to perceived side effects of. In the trazodone group, these effects included sedation, and eye discomfort.
Lipsey et al. 1984 **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	34 stroke patients with mild or major depression.	Participants were randomized to receive 20 - 100 mg nortriptyline (n=14) or placebo (n=20) for 6 weeks.	**Primary outcome:** Change in Hamilton Depression Scale (HDS) and Zung Depression Scale scores by end of treatment **Secondary outcome:** Response rate	Patients who were treated with nortriptyline showed significantly greater improvement on the HDS and Zung Scale. Among participants who completed the trial, the response rate was 100% for nortriptyline and 33% for placebo.
Pharmacotherapy for the Treatment of Post-stroke Anxiety with Co-morbid Depression					
Knapp et al. 2017 **UK** **Cochrane Review**	N/A	3 RCTs (n-196) including participants recovering from stroke who had been given a diagnosis of co-morbid depression and anxiety.	In trial one, patients were randomly assigned to treatment with paroxetine, paroxetine + psychotherapy or usual care. In trial two, patients were assigned to receive either buspirone hydrocholoride or usual care, and in trial 3, patients	**Primary outcomes:** Proportion of patients, following treatment, without a clinical diagnosis of anxiety based on the DSM (or other standard classification) and the proportion of patients scoring outside the symptom range as defined by the primary study	Trial 1: Based on Hamilton-Anxiety Rating scores (HAM-A), mean anxiety scores were significantly lower in both intervention groups when compared to the control group at 6 weeks (p<0.01). A similar trend was noted for depression scale scores. Mean HAM-A scores were reduced by 58% in the paroxetine condition and 71% in the paroxetine + psychotherapy condition. Trial 2: At the four-week assessment point, both

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			received four-week use of a relaxation CD.	author via anxiety rating scale or self-report.	groups had experienced a reduction in HAM-A anxiety scores. However, reduction in anxiety was significantly greater in the intervention group when compared to the usual care group ($p<0.01$). Treatment was also associated with a significant reduction in depressive symptoms. There was no information available regarding the treatment of anxiety only. Trial 3: 4/10 participants in the intervention group were no longer considered to have clinical levels of anxiety at three months, vs. 1/10 participant in the control group

Adjunct Therapies for the Treatment of PSD

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Light Therapy + Pharmacotherapy					
Sondergaard et al. 2006 **Denmark** **RCT**	CA: ☒ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☒	63 patients admitted to hospital following acute stroke who were diagnosed with major depression based on an assessment by a psychiatrist in accordance with the DSM-IV. Mean age was 75 years, 32% were male.	All patients were given a fixed dose of citalopram (20 mg) per day for 4 weeks. Patient participants were randomly assigned to receive either high (n=34) or medium (n=29) intensity light therapy. High intensity therapy was 10,000 lux daily at a distance of 30 cm while medium intensity treatment was defined as 4,000 lux daily at a distance of 60 cm. Light therapy was conducted every morning for 30 minutes over 14 days.	**Primary outcome:** Reduction of depression scores from baseline to week 4 on the Hamilton Rating Scale for Depression ($HAD\text{-}D_6$) **Secondary outcomes:** Reduction in depression scores on the $HAD\text{-}D_{17}$ and the Bech-Rafaelsen Melancholia Scale (MES)	Significantly more women were allocated to the high-intensity light group (26 vs. 3, $p<0.05$). All patients experienced similar reductions in reported symptoms of depression over the first 2 weeks of treatment. At two weeks, there were no significant between group differences reported on any of the three outcome measures (HAD-6, HAD-17 or MES). At 4 weeks, there was a statistically significant reduction in HRSD-6 scores in favour of the high intensity light treatment vs. moderate intensity (6.0 ± 3.0 vs. 4.4 ± 2.7, $p<0.05$). Although the differences did not reach statistical significance, higher-intensity light therapy was associated with greater reduction in depressive symptomatology using the other scales as well: 9.4 ± 4.2 vs. 7.7 ± 4.1 (HRSD-17) and 9.1 ± 4.4 vs. 7.1 ± 4.2 (MES). There were no significant side effects reported. No patients left the study due to side effects.
Talk-based Psychotherapy + Pharmacotherapy					
Alexopoulos et al. 2012 **USA**	CA:☒ Blinding: Patient	24 individuals diagnosed with post stroke depression (via SCI for DSM-IV-TR), MMSE ≥20. Individuals with mild to	Participants were randomly assigned to receive either ecosystem focused therapy (EFT) or education on	**Primary outcome:** Reduction of depression and disability. Severity of depression was quantified	Treatment X time analysis using a mixed effects linear model revealed an interaction suggesting that there was a trend toward greater decline in symptoms of depression associated with EFT vs. ESD or education

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	☒ Assessor ☒ ITT:☑	moderate aphasia could be included in the study. 58.3% of participants were male. Mean age was 70.9 ±8.5 years. Patients were recruited during inpatient rehabilitation following stroke	stroke and depression (ESD) for 12 weeks. EFT was provided in 12 weekly sessions of approximately 45 minutes in length. Inpatients had the first session prior to discharge; the remaining sessions were conducted in the participants' homes. EFT uses an integrated, educational, problem-solving approach to work through 5 therapy components – 1) provide an action-oriented perspective to recovery; 2) form a treatment "adherence enhancement structure" 3) provide a "problem solving structure" 4) help the family "re-engineer" to accommodate changed abilities and 5) coordinate with therapists and resources to develop a rehabilitation plan. Families and/or informal carers participated in sessions on an as-needed basis. Four therapists were trained in both EFT and ESD. All sessions were audiotaped.	using the HRSD. The WHODAS-II was also administered as an assessment of function. Assessments were conducted at baseline, weekly during throughout the study.	(p=0.054). The mean HRSD score at 12 weeks was 8.2 (sd=6.63) for individuals in the intervention group and 13.2 (sd=5.37) for individuals assigned to the education control group. Remission of depression was recorded for 8/12 participants receiving EFT (66.7%) vs. 2/12 (16/7%) participants in the education group (OR = 10, 95% CI 1.44, 69.26). The standardized between group effect size at the end of the intervention was 0.83 (95%CI =0.07, 1.72). In terms of disability, assignment to the EFT group was associated with greater gains in function over time (p=0.015). At 12 weeks, the standardized effect size between groups was 0.53 (95% CI -0.36, 1.43). 7/12 patients in the EFT condition and 5/12 patients in the ESD condition were treated with antidepressants at some point during the 12-week intervention period.
Mitchell et al. 2009 **USA** **RCT**	CA: ☒ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☑	101 patients recruited within 4 months of an ischemic stroke event and who were verified as depressed following a diagnostic interview based on the DSM-IV criteria. Mean age was 57 years, 59% male. Approximately 70% reported one episode of pre-stroke depression. 60% were taking an antidepressant at the time of study entry.	Patients were randomized to receive either a brief psychosocial, problem-solving intervention + possible antidepressant medication (n=48) or usual care + possible antidepressant medication (n=53). The psychosocial intervention consisted of 9 sessions over 8 weeks of problem-solving therapy and increased pleasant social and physical activity provided by a study (nurse) interventionist. Patients	**Primary outcome:** Reduction in the severity of depression symptoms, assessed using the Hamilton Depression Scale (HDS) at 12 months post stroke, remission of depression at 12 months (HDS<10) **Secondary outcomes:** Stroke Impact Scale SIS) at 12 months	At one year, the mean decrease in symptoms of HDS scores was significantly greater in the treatment group than in the control group (-9.2±5.7 vs. -6.2±6.4, p=0.023). At 24 months, there was no longer a significant difference between groups. Assignment to the treatment condition was associated with significantly greater odds for remission of depression immediately following treatment (OR=4.8, 95% CI 1.8- 12.9, p=0.001), at 21 weeks (OR=3.4, 95% CI 1.3- 8.7, p=0.008) and at 12 months (OR=2.7, 95% CI 1.1- 6.6, p=0.031), but not at 24 months. At 12 months, participants who achieved remission had significantly better total SIS scores compared to those who remained depressed (74.5 vs. 52.6,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			allocated to usual care were treated by stroke care provider.		p<0.01). 77% of each group reported the use of an antidepressant during the 8-week intervention period. The most commonly prescribed drugs were sertraline, citalopram and paroxetine.
Lincoln & Flannaghan 2003 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT:☒	123 stroke patients identified via hospital records who were either living at home, in hospital or living in long-term care one-month post stroke with >10 score on Beck Depression Inventory (BDI) or >18 on Wakefield Depression Inventory (WDI). There were 60 patients with a primary diagnosis of major depression at baseline. Mean age of patients was 65 ±15.1 in the no intervention group, 66.1±13.2 in the attention group and 67.1±12.7 in the CBT group. 51% of participants were male. Potential participants were excluded if they scored ≤23 on the MMSE.	Participants were randomly allocated to one of 3 conditions: 1) no intervention (n=41), 2) attention placebo (n=43) and 3) CBT (n=39). Patients in condition 1 had no further contact with the community psychiatric nurse. Patients in the attention placebo (2) condition received 10, 1-hour visits over 3 months by the community psychiatric nurse in which they discussed daily life, consequences and changes associated with stroke. In the CBT (3) condition, participants received 10, 1-hour sessions over 3 months by the community psychiatric nurse who used techniques such as education, graded task assignment, activity scheduling and identification and modification of unhelpful thoughts/beliefs – tailored to individual participants.	**Primary outcomes:** BDI and WDI **Secondary outcomes:** EADL scale, LHS and a rating of satisfaction of care. Assessments were conducted at baseline, 3- and 6-months post-randomization.	Examination of between group differences at baseline revealed no significant differences except that there were significantly more individuals with a diagnosis of major depression (ICD-10) allocated to receive CBT than either attention control or no intervention (p<0.05), although there were no significant differences in the BDI or WDI scores between groups at the time of study entry (p=0.2 and p=0.2, respectively). Mean number of CBT sessions delivered to participants was 9.85 (±2.31). Mean number of attention control sessions delivered was 10 (±0.55), but there was no significant between group difference reported in number of sessions received. For the primary study outcomes, the authors reported no significant difference on either the BDI or WDI at 3 months (p=0.5, p=0.9, respectively) or at 6-month follow-up (p=0.6, 0.4, respectively). 32% of the patients recruited did receive antidepressant therapy at some point during the study period. No between group differences were found in terms of the proportion of participants receiving antidepressant therapy.
Active Care Management					
Williams et al. 2007 **USA** **RCT**	CA: ☑ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☑	188 patients ≥18 years, 1-2 months following ischemic stroke, with verified mild or major depression following a diagnostic interview based on the DSM-IV criteria. Mean age was 60 years, 45% were male.	Patients were randomly allocated to receive either the Activate-Initiate-Monitor (AIM) intervention n=94 or control conditions, n=94. The AIM intervention consisted of 3 steps: 1) *activate*-stroke survivors underwent a 20-minute psycho-educational session	**Primary outcome:** Proportion of responders to treatment at 12 weeks (defined as Hamilton Depression Scale (HAM-D) score <8, or a 50% or more decrease in HDS score. **Secondary outcomes:** Depression remission (HAM-D score <8 or, PHQ-9 score <5),	A significantly higher percentage of persons in the AIM group responded to treatment (51% vs 30%, p=0.005), and experienced remission (39% vs. 23%, p=0.01) at 12 weeks. Mean change from baseline to 12 weeks was not significantly greater for persons in the AIM group, assessed using the HAM-D (-7.3 ±7.2 vs. -5.3±8.0; p=0.07), but was significantly greater when assessed by PHQ-9 (-8.0±6.2 vs. -5.0 ±6.4, p=0.002).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			at baseline; 2) *initiate* antidepressant medication and 3) monitor treatment effectiveness (including dose adjustment and medication change as necessary via scripted bi-monthly telephone calls). The control condition consisted of usual care plus an identical number of baseline and telephone sessions as were received by the treatment condition in order to control for an attention effect. 56% of persons in the control group took an antidepressant during the study period.	and reduction in severity of symptoms, measured by mean change in HAM-D or PHQ-9 scores at 12 weeks.	Serious events were reported in 17 participants, but event rates were not significantly different between groups. 15 participants in the intervention group reported antidepressant-related side effects that prompted a medication change and 4 individuals reported more than one such change. 39 medication-related effects were reported, the most common of which were sedation, sexual, gastrointestinal and anxiety-related effects.

Pharmacotherapy and Functional Recovery

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dennis et al. 2019 **UK** **RCT** ***Fluoxetine Or Control Under Supervision (FOCUS) trial***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☒	3,127 patients recruited from 103 hospitals, ≥18 years with a clinical diagnosis of stroke, who were enrolled between 2 days and 15 days post onset. Mean age was 71 years, 61% were men.	Patients were randomized 1:1 to receive 20 mg fluoxetine or placebo orally once daily for 6 months.	**Primary outcome:** (ordinal) mRS scores at 6 months **Secondary outcomes:** Survival at 6 and 12 months, mRS scores at functional status at 12 Stroke Impact Scale scores at 12 months, Mental Health Inventory (MHI-5), the Vitality subscale of SF3 and the EuroQoL-5 Dimensions-5 Levels (EQ5D-5L)	*6-month follow-up* There was no significant difference between groups in the distribution of mRS scores (common OR= 0·951, 95% CI 0·839–1·079, p=0·439), nor was there a significant difference in proportions when mRS scores were dichotomized (0–2 vs. 3–6). There were no significant differences between groups based on all sub groups analyses. A lower percentage of patients in the fluoxetine group were likely to be diagnosed with new depression (13·4% vs. 17.2%; difference in proportions of 3·78%, 95% CI 1·26–6·30, p=0·0033). Median MHI-5 scores were significantly higher in the fluoxetine group (76 vs. 72, p=0·0100). There were no significant differences in any other secondary outcomes.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The risk of bone fractures was significantly higher in the fluoxetine group 2·88% vs.1·47%, p=0·0070), as were the number of epileptic seizures (3.8% vs. 3.5%, p=0.03). *12-month outcomes* The distribution of mRS scores between groups was not significantly different, nor was there a significant difference in proportions when mRS scores were dichotomized (0–2 vs. 3–6). There were no significant differences between groups in survival, median SIS scores, MHI-5, EQ5D-5L, or new onset depression.
Mead et al. 2012 **UK** **Cochrane Review**	NA	56 RCTs (n=4,060) including participants who were recovering from stroke that occurred within the previous 12 months. Mean age of participants ranged from 55-77 years. The majority of trials recruited participants within 3 months of stroke. A diagnosis of depression was an inclusion criterion in 35 trials.	Trials compared treatment with SSRIs, given for any period of time, at any dose to usual care or placebo in patients with stroke. Trials using a cross-over design, that compared different active treatments, or recruited participants with a mean time since stroke >12 months were excluded. The most commonly used agents were fluoxetine (n=28), paroxetine (n=10), sertraline (n=7)	**Primary outcome**: Disability and dependence at the end of treatment. **Secondary outcomes**: Impairment, depression, anxiety, quality of life, and fatigue.	Dependency: On the basis of a single trial (FLAME), SSRIs were found to be significantly associated with reduced dependency (RR=0.81, 95% CI 0.68 to 0.97). Disability: On the basis of 22 trials (n=1310), a non-significant trend in favor of SSRIs was reported (SMD=0.92, 95% CI 0.62 to 1.23). Neurological deficit: on the basis of 29 trials (n=2011), results significantly favoured SSRIs (SMD=-1.0, 95% CI -126 to -0.75). Depression: Results favoured SSRIs whether based on continuous measures of depression (SMD=-1.91, 95% CI -2.34 to -1.48) or dichotomous measures of depression (R=0.43, 95% CI 0.24 to 0.77). Results were based on 39 (n=2728) and 8 trials (n=771), respectively.
Chollet et al. 2011 **France** **RCT** ***Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)***	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	118 patients, aged 18-85 years, free from clinical depression and not taking any anti-depressant medication enrolled within 5 to 10 days of stroke with Fugl-Meyer Motor Scale (FMMS) scores of <55. Mean age was 65 years, 61% were men.	A mean of 9 days after stroke, participants were randomized 1:1, 5-10 days post-stroke to receive fluoxetine (20 mg/day) or placebo for 90 days. All participants received physiotherapy and standard inpatient stroke care during the study period.	**Primary outcome:** FMMS scores at day 90. **Secondary outcomes:** NIHSS, modified Rankin Scale, and the Montgomery Asberg Depression Ration Scale at 90 days.	At the end of the 90-day treatment period, participants who received fluoxetine demonstrated significantly greater mean improvement on the FMMS, controlling for centre, age, history of stroke, and baseline FMMS (9.8 points, 95% CI 3.4-16.1, p=0.003). Participants who received fluoxetine also demonstrated significantly greater mean improvement on the FMMS upper sub scale scores (9.7 points, 95% CI 3.6-15.9, p=0.02), and the lower sub scale (3.3 points, 95% CI 0.8-5.7, p=0.01). Two serious adverse events occurred in the fluoxetine group (hyponatraemia and partial seizure). Transient digestive disorders (nausea, diarrhea, and abdominal

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					pain) were more common in the active treatment group (25% vs. 11%). There were 2 drop-outs in the fluoxetine group and 3 in the placebo group.

Pharmacotherapy for Treatment of Post-Stroke Emotionalism

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hackett et al. 2010 **Cochrane Review**	N/A	7 RCTs (representing 239 patients), including participants with established emotionalism at study entry following stroke. Mean or median age of participants ranged from 57.8 to 73 years. Timing from stroke to study entry ranged from 3 days to 13 years.	Treatments compared any pharmacological agent vs. placebo for the treatment of emotionalism post stroke. Studies in which treatment was primarily targeted stroke-associated pain syndrome or depression were excluded, even if emotionalism was assessed as a secondary outcome. 5 trials evaluated SSRIs and 2 evaluated TCAs.	**Primary outcomes:** Percentage of patients achieving ≥ 50% reduction in emotionalism, reduced tearfulness, clinical impression of change, and improvement on measures assessing emotional lability.	Most data came from 5 trials, representing 213 patients. The odds of achieving a 50% reduction in emotionalism were significantly increased in the treatment group (OR= 63.0, 95% CI 2.63 – 1511.41). Results from a single trial included. The odds of improvement (i.e. reduction) in tearfulness were significantly increased in the treatment group. (OR=9.35, 95% CI 4.26 – 20.54). Results from 4 trials included. Drug class did not appear to impact the effectiveness of treatment.

Pharmacotherapy for the Treatment of Post-Stroke Apathy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Starkstein et al. 2016 **Australia** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑	13 patients (out of 20 eligible) aged ≥40 and <90 years, who had sustained a recent stroke and met the criteria for apathy 8 weeks later (based on a score of ≥14 on the Apathy Scale), without depression, dementia, or severe aphasia. Mean age	13 participants were randomized to receive 900 mg nefiracetam (n=6) or placebo (n=7) daily for 12 weeks.	**Primary outcomes:** Change in Apathy Scale (AS) scores at 12 weeks	Mean AS scores at baseline were 23.0 (placebo) and 20.5 (nefiracetam), p=0.42. At 12 weeks, the mean changes in AS scores were -7.6 (placebo) and -6.3 (nefiracetam), Δ=1.2, 95% CI -14.8-17.2), which was not significantly different. There were 4 2 cases of severe adverse events in the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	ITT: ☑	was 69 years, 77% were male.			placebo group vs. 5 in the nefiracetam group.
Robinson et al. 2009 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	70/159 patients diagnosed with major depression who completed 12 weeks of treatment with nefiracetam (Robinson et al. 2008), who also met the criteria for apathy (based on Apathy Scale scores). Mean ages were 64.7, 63.9 and 70.5 in the placebo and 2 treatment groups, respectively. 53.5% were female. There were no significant between group differences noted at baseline.	Participants were randomly assigned to receive 1 of 3 treatments for 12 weeks: i) 600 mg nefiracetam (n=26), ii) 900 mg nefiracetam (n=22) or iii) matching placebo.	**Primary outcome:** Change in Apathy Scale scores **Secondary outcome:** Apathy remission, defined as a 75% reduction in Apathy Scale scores	Mean baseline Apathy Scale scores across groups were 19.3, 20.3 and 21.2. Patients receiving 900 mg/day of nefiracetam showed a significantly greater decrease in Apathy Scale scores during the 12-week trial compared to patients receiving placebo (p<0.01). Patients receiving 600 mg/day of nefiracetam did not show a significantly greater decrease in Apathy Scale scores during the 12-week trial compared to patients receiving placebo (p=0.29). Remission was achieved by 4/22 patients in the 900 mg group, 1/26 patients in the 600 mg group and 0/22 in the placebo group (p=0.031).

Pharmacotherapy for the Prevention of Post-Stroke Depression & Anxiety

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews & Meta-analyses					
Salter et al. 2012 **Canada** **Systematic Review**	N/A	8 RCTs trials that examined prevention of post-stroke depression (PSD) via comparison of pharmacotherapy with a control condition. Participants were limited to individuals with no clinically diagnosable PSD at study entry.	All trials were placebo controlled. Classes of active agents examined included SSRIs, tricyclic antidepressants, tetracyclic antidepressants and atypical antidepressants	**Primary outcome:** The development of PSD at the end of treatment.	Interview-based assessments were used to determine the presence/absence of depression in all studies except one that used the HADS. Pooled analysis, based on 776 observations, demonstrated a significantly reduced risk for development of PSD associated with the use of prophylactic pharmacotherapy (OR=0.34, 95% 0.22-0.53, p<0.001). In a sensitivity analysis, including the 5 trials with treatment duration of 1 years, there was a significant reduction in odds for PSD (OR=0.31, 95% CI 0.18, 0.56; p<0.001). The most commonly reported side effects in t studies that did report them were tiredness/fatigue, dizziness and gastrointestinal upsets (most often nausea and diarrhea).
Yi et al. 2010	NA	6 trials (3 English, 3 Chinese)	Trials compared the use of	**Primary outcome:**	Only 3 studies provided data on the development of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
China **Systematic Review**		including study participants confirmed as having no diagnosis of depression following stroke, at study entry.	fluoxetine in the prevention of post-stroke depression (PSD) vs. placebo (n=3) or no treatment conditions (n=3). Duration of intervention ranged from 4 to 12 weeks.	Incidence of PSD	new onset depression in treatment vs. control conditions (n=176). Treatment with fluoxetine was associated with a significantly reduced risk of the development of PSD (OR=0.25, 95% CI 0.11-0.56, p=0.0009). Analysis of symptom severity suggested that active treatment was associated with a non-significant reduction in symptoms (WMD=-3.97, 95% CI-9.85-1.9). Drop-out rates attributable to adverse events ranged from 0% to 11.1% in groups assigned to fluoxetine treatment and 0% to 14.3% in comparison groups. Drop-out rates were similar between groups
Hackett et al. 2008 **Australia** **Cochrane Review**	NA	14 RCTs (n=1,515), which included participants without a diagnosis of depression who had experienced a stroke, recruited from hospitals, outpatient clinics or from home. The mean or median age of the participants ranged from 55 to 74 years.	10 trials (12 comparisons) examined the use of a variety of pharmacological agents vs. placebo. Treatment duration varied from 2 weeks to 12 months. Treatment contrasts included SSRI vs. placebo, serotonin antagonist and reuptake inhibitor vs. placebo. Other agents included piracetam, maprotiline, mianserin, nortriptyline, indeloxazine and methylphenidate,	**Primary outcome:** Proportion of patients who met the criteria for depression at the end of study, or study follow-up. **Secondary outcomes:** Depression scale scores, psychological distress, cognition, social activities	6/10 trials reported numbers of participants meeting the criteria for depression at the end of the study intervention. This proportion appeared to be lower in groups of individuals assigned to treatment with a prophylactic antidepressant; however, no pooled analysis was performed because of the wide variety of study methods and assessment tools used. Pooled analyses were not carried out for pharmacological interventions. When between-group differences in continuous scores on depression scales were considered, *there was no evidence of benefit of pharmacotherapy for mean scores at the end of treatment or change in mean scores from baseline. There was no evidence of benefit of pharmacotherapy improving cognitive function or activities of daily living (ADL), or reducing disability* There was also no clear evidence of harm based on reporting of adverse events.
Chen et al. 2007 **USA** **Systematic Review**	NA	10 RCTs including participants confirmed as having no diagnosis of post stroke depression (PSD).	Trials compared the use of a single antidepressant agent (SSRI=6, TCA=2 and other agents=5) with a control condition for the prevention of PSD. The duration of treatment ranged from 4 -52 weeks (mean ± SD: 19.2 ± 19.3 weeks).	**Primary outcome:** Incidence of PSD **Secondary outcome:** Depression severity	The occurrence of PSD was significantly lower in the intervention group (12.54% vs. 29.17%; rate difference=-0.17, 95% CI -0.26, to -0.08, n=8 trials). Both SSRI use and TCA use was associated with reductions in the occurrence rate of PSD (rate difference= – 0.12, 95% CI – 0.20 to – 0.04 and – 0.23, 95% CI – 0.44 to – 0.11, respectively). Reductions in rate did not appear to be associated with the interval between onset of stroke and the beginning

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					of the prophylactic intervention. There was no significant difference in the reduction of symptom severity between groups. At baseline, the weighted mean difference in depression rating scale scores between the intervention and control groups was 1.0, 95% CI: 0.0 to 2.0). At endpoint, the pooled WMD was – 0.5 (95% CI: – 1.5 to 0.5) between group (n=n/s).
Clinical Trials					
Mikami et al. 2014 **USA** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	176 patients from Robinson et al. 2008. (27 with generalized anxiety disorder identified at baseline, were excluded from the current analysis). 149 patients were aged 50-90 years recovering from ischemic or haemorrhagic stroke occurring within the previous 3 months, who were not diagnosed with depression or anxiety.	As per Robinson et al. 2008. Patients were randomly assigned to receive 1 of 3 treatments: i) escitalopram 10 mg/d (if <65 yrs, 5 mg/d for patients ≥ 65, n=59) ii) matching placebo, n=58 or iii) problem-solving therapy (PST), n=59, (6 treatment sessions over 12 weeks + 6 reinforcement sessions over 9 months). The problem-solving therapy used in this study was a manual-based intervention developed in the UK. All sessions were videotaped and evaluated for adherence.	**Primary outcome:** Risk of developing generalized anxiety disorder (GAD), adjusting for age, gender, previous history of GAD and FIM	At the end of 12 months, there were 9 cases of GAD in patients who received placebo vs. 2 cases for those who received escitalopram and 3 who received PST. Compared with escitalopram, patients who received placebo were significantly more likely to develop GAD (HR=4.95, 95% CI 1.54-15.93, p=0.007). Compared with PST, patients who received placebo were significantly more likely to develop GAD (HR=4.00, 95% CI 1.84-8.7, p=0.0005). There were 7 patients with GAD and comorbid depression. There were 7 patients with GAD, but without depression. There were 5 cases of GAD (-depression) in patients who received placebo vs. 0 cases for those who received escitalopram and 2 who received PST. After combining the results from the 2 active treatment arms, the risk of developing GAD was significantly higher for patients who received placebo (HR=6.63, 95% CI 2.85-15.4, p<0.0001).
Zhang et al. 2013 **China** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	95 patients, aged 40-80 years, admitted to a neurology unit following acute ischemic stroke, without a psychiatric disorder. Mean age was 64 years, 55% were male.	Following a comprehensive assessment battery, participants were randomly assigned to receive either treatment with duloxetine (30 – 90 mg/day; n=49) or a placebo (n=48) for 12 weeks, in addition to routine therapy.	**Primary outcome:** Minor and major depression, defined as scores of 8-17 (minor) and >17 (major) using the Hamilton Depression Scale (HDS) **Secondary outcomes:** Changes in scores from baseline to 24 weeks) in HDS, NIHSS, MMSE, the ADL (Chinese version) and SF-36	The incidences of minor and major depression were significantly lower in the duloxetine group (28.6 vs. 12.5%, p=0.05 and 24.5 vs. 8.3%, p<0.05, respectively). At 24 weeks, the use of duloxetine was associated with significantly improved scores on all other assessments. There were 21 dropouts (n=12 duloxetine, n=9 control). Nausea and vomiting were the most commonly-reported side-effects.
Chollet et al. 2011	CA: ☑	118 patients, aged 18-85 years,	Participants were	**Primary outcome:**	The incidence of depression was significantly lower in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
France **RCT** ***Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)***	Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	free from clinical depression and not taking any anti-depressant medication enrolled within 5 to 10 days of stroke with Fugl-Meyer Motor Scale (FMMS) scores of <55. Mean age was 65 years, 61% were men.	randomized 1:1, 5-10 days post-stroke to receive fluoxetine (20 mg/day) or placebo for 90 days. All participants received physiotherapy and standard inpatient stroke care during the study period.	FMMS scores at day 90 (results reported above). **Secondary outcomes:** NIHSS, modified Rankin Scale, and the Montgomery Asberg Depression Ration Scale at 90 days.	the fluoxetine group (7% vs. 29%, p=0.002). After adjustment for age, history of previous stroke and baseline FFMS scores there was a significant difference reported in mean change in symptoms of depression. Over the treatment period, there was no change in depressive symptomatology within the treatment group (adjusted mean change = -0.1, 95% CI -2.1 to 1.9) while there was a significant increase in symptoms in the placebo group (adj. Mean change = 3.2, 95% CI 1.1-5.3, p=0.032). Two serious adverse events occurred in the fluoxetine group (hyponatraemia and partial seizure). Transient digestive disorders (nausea, diarrhoea, and abdominal pain) were more common in the active treatment group (25% vs. 11%).
Tsai et al. 2011 **Taiwan** **RCT**	CA:☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	92 patients admitted to a neurology unit following first or recurrent ischemic stroke (within the preceding 4 weeks) and no depression. Individuals with previous depression, those taking antidepressants or with possible, undiagnosed depression (HAM-D≥10) were excluded from the study	Study participants were randomized to receive either 50 mg milnacipran (titrated to 100 mg by one week of treatment) per day, or matching placebo for 1 year.	**Primary outcome:** Incidence of post-stroke depression (PSD), diagnosed using DSM IV criteria.	56 participants (60.9%) completed the study. Overall, 8 participants developed PSD during the treatment period – only one of whom was assigned to the active treatment condition. The incidence of PSD was significantly lower in the treatment group (2.2% vs. 15.2%, p=0.048). Side effects were reported by both groups – there was no significant between group difference reported for study withdrawal due to side effects (p=0.73). The main reason for study withdrawal was reported to be difficulty in following the study protocol, not side effects associated with treatment. In total, 7/21 patients who withdrew from the active treatment group did so because of reported side effects.
Robinson et al. 2008, 2017 **Mikami et al. 2011** **USA** **RCT**	CA:☑ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☑	176 patients, aged 50-90 years recovering from ischemic or haemorrhagic stroke occurring within the previous 3 months, who were not diagnosed with depression. Depression was assessed using the DSM-IV criteria or a score >11 on the Hamilton Depression Scale. Mean ages across treatment groups ranged from 61-97 years, 59.7% of participants were male.	Patients were randomly assigned to receive 1 of 3 treatments: i) escitalopram 10 mg/d (if <65 yrs, 5 mg/d for patients ≥ 65, n=59) ii) matching placebo, n=58 or iii) problem-solving therapy (PST), n=59, (6 treatment sessions over 12 weeks + 6 reinforcement sessions over 9 months). The problem-solving therapy used in this study was a manual-based intervention developed in the UK. All sessions were	**Primary outcome:** The onset of diagnosable major or minor depression, diagnosed using DSM-IV criteria at 12 months. **Secondary outcomes:** FIM, neuropsychological tests Assessments were conducted at 3, 6, 9 and 12 months.	At one year, in the per-protocol analysis, adjusted for previous history of mood disorders, patients assigned to the placebo condition were more likely to develop depression than individuals receiving either therapy with escitalopram (adj. HR= 4.5, 95% CI 2.4-8.2, p<0.001; or problem-solving therapy (adj. HR=2.2, 95% CI 1.4-3.5, p<0.001). The results were similar in the intention-to-treat analysis that included 27 patients who did not receive any treatment. Escitalopram was superior to placebo (23.1% vs. 34.5%, HR = 2.2 95% CI 1.2-39, p=0.007); however, problem-solving therapy was not (30.5% vs. 34.5%, HR=1.1, 95% CI 0.8-1.5, p=0.51).

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			videotaped and evaluated for adherence.		All patients experienced improvement in ADLs over time, but there were no significant time x treatment group interactions. There were no between group differences for any of the adverse events reported (decreased libido, fatigue, and GI symptoms). There was no evidence that patients receiving problem-solving therapy were more or less likely to be hospitalized with illness of cardiovascular origin than individuals receiving escitalopram. **2011 follow-up study** During the 6 months after cessation of treatment, 108 participants were available for evaluation. The incidence of new onset major depression was significantly higher for participants initially randomized to receive escitalopram (4 cases (11.8%) vs. 0 for placebo (p=0.114) and 0 for PST (p=0.038). Mean Hamilton Depression Scale scores were significantly higher for patients who received escitalopram compared with those who received placebo or PST (6.8 vs. 4.5 or 4.0, p=0.007, respectively). **2017 follow-up** A mean of 8 years following the end of treatment, 122 participants were available. Participants who received PST were significantly less likely to have died (HR= 0.4625), compared with the combined group of escitalopram + placebo. Increasing age and the development of depression were significant predictors or mortality.
Almeida et al. 2006 **Australia** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	111 patients recovering from acute stroke (within previous 2 week) without severe cognitive impairment, aphasia or depression. Mean age was 67.5 years, 65% were male. Mean baseline Hospital Anxiety & Depression Scale (HADS-D) score was 3.2	Participants were randomly assigned 1:1 to receive treatment with sertraline (50 mg/day) or a matching placebo for 24 weeks.	**Primary outcome:** Development of significant symptoms of depression (HADS-D≥8 or diagnosed through clinical examination) at 24 weeks **Secondary outcomes:** Changes in HADS-D, MMSE and mRS scores at 24 and 52 weeks	At 24 weeks, 21.6% of patients assigned to the placebo group and 16.7% of patients assigned to treatment with sertraline were diagnosed with depression (OR = 0.8, 95% CI 0.3-2.1, p=0.59). Trial medication was stopped in 51.8% (placebo) and 47.3% (sertraline), mostly due to reported side effects. At 52 weeks, 30% in the placebo group vs. 22.7% in the active treatment group met the criteria for depression (p=0.43).

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					There were no significant differences in scores on any of the secondary outcomes, assessed at either 24 or 52 weeks.
Rasmussen et al. 2003 **Denmark** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	137 patients admitted to the neurology units of a hospital system following stroke that occurred within the preceding 4 weeks, without depression. Individuals with significant aphasia or cognitive impairments (dementia) were excluded. Mean age was 70 years, 60% were men.	Participant were randomly assigned to treatment with sertraline (a maximum dose of 150 mg/day/, n=70) or matching placebo (n=67) for a period of one year.	**Primary outcome:** Development of depression, diagnosed as a score >18 on the Hamilton Depression Scale (HDS-D)-17, or ≥9 on the HDS-6, or >16 on the Geriatric Depression Scale (GDS)	At baseline the mean HDS-17 was significantly higher in the placebo-treated group (7.6 vs. 6.5, p<0.05). After 52 weeks, a significantly lower number of patients treated with sertraline developed depression, based on HAD-17 criteria (8.2% vs. 22.8%, p<0.05). Treatment superiority was evident after 21 weeks. Treatment with sertraline was also significantly more effective in preventing depression, assessed using HDS-6 criteria. (11.5% vs. 28.1%, p<0.05). Treatment superiority was evident after 6 weeks. Treatment with sertraline was also significantly more effective in preventing depression, assessed using GDS criteria, where treatment superiority was evident after 20 weeks There were no significant differences between groups in terms of the frequency of reported effects. There were fewer patients in the active treatment group who reported severe cardiovascular and noncardiovascular events. Incidence of diarrhea and nausea were 5% higher among individuals treated with sertraline.

Pharmacotherapy for the Prevention of Post-Stroke Apathy

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Mikami et al. 2013 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	159/176 patients included in Robinson et al 2008, without evidence of apathy. The identification of apathy was based on a loss of motivation and at least two other symptoms from the Apathy Scale.	As per Robinson et al. 2008. Patients were randomly assigned to receive 1 of 3 treatments: i) escitalopram 10 mg/d (if <65 yrs, 5 mg/d for patients ≥ 65, n=51) ii) matching placebo, n=47 or iii) problem-solving therapy (PST), n=56, (6 treatment sessions over 12 weeks + 6 reinforcement sessions over 9 months). The problem-	**Primary outcome:** Risk of incident apathy at 1 year	There were 14 cases of apathy among patients in the placebo group, 5 cases in the escitalopram group, and 11 cases in the PST group. The mean time from stroke onset to apathy ranged from 5-6.3 months. After adjustment for age, sex, baseline total Repeatable Battery for the Assessment of Neuropsychological Status score, and the presence or absence of diabetes, the risk of developing apathy was significantly higher among patients in the placebo group compared with those who received escitalopram (HR=3.47, 95% CI 1.79-6.73) and those who received PST (HR=1.84, 95% CI 1.21-2.80)

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			solving therapy used in this study was a manual-based intervention developed in the UK. All sessions were videotaped and evaluated for adherence.		After excluding 10 patients with comorbid depression, the risk of developing apathy remined similar for patients who received placebo compared with those who received either escitalopram (HR=3.49, 95% CI 1.37-8.90) or PST (HR= 2.25, 95% CI 1.51-3.36). The frequency of adverse events was similar between groups (escitalopram vs. PST+ placebo)

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