Journal of Affective Disorders 235 (2018) 589–596

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Cognitive behavioral therapy for post-stroke depression: A meta-analysis

Shi-Bin Wang[a,1], Yuan-Yuan Wang[b,1], Qing-E Zhang[c,1], Shuo-Lin Wu[d,e,1], Chee H. Ng[f], Gabor S. Ungvari[g], Liang Chen[b], Chun-Xue Wang[d,e], Fu-Jun Jia[a], Yu-Tao Xiang[b,*]

[a] Guangdong Mental Health Center, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[b] Unit of Psychiatry, Faculty of Health Sciences, University of Macau, 3/F, Building E12, Avenida da Universidade, Taipa Macau, SAR, China
[c] The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
[d] Department of Neuropsychiatry and Behavioral Neurology and Clinical Psychology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[e] China National Clinical Research Center for Neurological Diseases, Beijing, China
[f] Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
[g] The University of Notre Dame Australia/Graylands Hospital, Perth, Australia

ARTICLE INFO

Keywords:
Cognitive behavioral therapy
Post-stroke depression
Meta-analysis

ABSTRACT

Background: Cognitive behavioral therapy (CBT) has been widely used for post-stroke depression (PSD), but the findings have been inconsistent. This is a meta-analysis of randomized controlled trials (RCTs) of CBT for PSD.
Methods: Both English (PubMed, PsycINFO, Embase) and Chinese (WanFang Database, Chinese National Knowledge Infrastructure and SinoMed) databases were systematically searched. Weighted and standardized mean differences (WMDs/SMDs), and the risk ratio (RR) with their 95% confidence intervals (CIs) were calculated using the random effects model.
Results: Altogether 23 studies with 1,972 participants with PSD were included and analyzed. Of the 23 RCTs, 39.1% (9/23) were rated as high quality studies, while 60.9% (14/23) were rated as low quality. CBT showed positive effects on PSD compared to control groups (23 arms, SMD = −0.83, 95% CI: −1.05 to −0.60, $P < 0.001$). Both CBT alone (7 arms, SMD = −0.76, 95% CI: −1.22 to −0.29, $P = 0.001$) and CBT with antidepressants (14 arms, SMD = −0.95, 95% CI: −1.20 to −0.71, $P < 0.00001$) significantly improved depressive symptoms in PSD. CBT had significantly higher remission (6 arms, RR = 1.76, 95% CI: 1.37–2.25, $P < 0.00001$) and response rates (6 arms, RR = 1.41, 95% CI: 1.22–1.63, $P < 0.00001$), with improvement in anxiety, neurological functional deficits and activities of daily living. CBT effects were associated with sample size, mean age, proportion of male subjects, baseline depression score, mean CBT duration, mean number of CBT sessions, treatment duration in each session and study quality.
Conclusion: Although this meta-analysis found positive effects of CBT on depressive symptoms in PSD, the evidence for CBT is still inconclusive due to the limitations of the included studies. Future high-quality RCTs are needed to confirm the benefits of CBT in PSD.

1. Introduction

Post-stroke depression (PSD) which is a debilitating neuropsychiatric complication, affects about a third of stroke survivors (Hackett and Pickles, 2014; House et al., 1991). Apart from the stroke-related neuroanatomical damage (Broomfield et al., 2011), the sensorimotor and behavioral impairments that significantly restrict activities of daily living are also contributing factors of PSD (Kootker et al., 2015). Common risk factors of PSD include age, gender, medical and psychiatric history, comorbidity, type and severity of stroke, location of lesion, genetic factors, level of disability and social support (Broomfield et al., 2011; Robinson and Jorge, 2016). There is a complex interplay of PSD with other comorbidities, such as anxiety, cognitive impairment, neurological functional deficits and obstructive sleep apnea, which in combination could result in severe functional impairment, reduction of quality of life, stroke recurrence and mortality (Bays, 2001; Robinson and Jorge, 2016; Swartz et al., 2016; van Mierlo et al., 2016).

Although anti-depressants have been recommended for the treatment of PSD, the efficacy and safety of pharmacotherapy in PSD remain controversial (Cadilhac et al., 2017; Hackett et al., 2005). For example, a meta-analysis found that the use of selective serotonin reuptake inhibitors (SSRI) was associated with increased risk of intracerebral and

* Corresponding author.
E-mail address: xyutly@gmail.com (Y.-T. Xiang).
[1] These authors equally contributed to the work.

https://doi.org/10.1016/j.jad.2018.04.011
Received 7 October 2017; Received in revised form 3 March 2018; Accepted 2 April 2018
Available online 05 April 2018
0165-0327/

intracranial hemorrhage (Hackam and Mrkobrada, 2012). On the other hand, other meta-analyses found that pharmacotherapy was associated with complete remission or improvement of depressive symptoms in PSD (Hackett et al., 2008; Mead et al., 2012) although it was also associated with a high risk of adverse events (Hackett et al., 2008). Cognitive behavioral therapy (CBT) has shown comparable effects to pharmacotherapy in the treatment of moderate-severe depression in the general population (DeRubeis et al., 2005). The therapy helps patients regulate their emotions, achieve optimal levels of activities and functioning, and maintain realistic and optimistic thinking (Broomfield et al., 2011). Apart from depression, adjunctive CBT is also effective for anxiety, schizophrenia, personality disorders, bipolar disorder, insomnia, pain management, and medical conditions related stress (McMain et al., 2015). In comparison to pharmacotherapy, CBT is associated with lower relapse rate and lack of side-effects (Broomfield et al., 2011).

Given its advantages, CBT has been widely used for the treatment of PSD but the findings have been inconsistent (Gao et al., 2017; Kootker et al., 2017; Lincoln and Flannaghan, 2003). A number of randomized controlled trials (RCTs) conducted in China, either of CBT alone or CBT combined with antidepressants for PSD, have shown a positive effect in PSD (Yuan and Li, 2015; Zhou and Wang, 2015). Outside China, only a few RCTs have been published (Kootker et al., 2017; Lincoln and Flannaghan, 2003) with small to moderate sample sizes. To date, no meta-analysis on the efficacy of either CBT alone or in combination with antidepressants in PSD has yet been published. Therefore, we aimed to conduct a systematic review and meta-analysis of RCTs of CBT in PSD, including RCTs in Chinese language that is not well-known to Western researchers.

2. Methods

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number of CRD42017064824.

2.1. Inclusion and exclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009), the inclusion criteria were constructed (assembled, put together) using the PICOS acronym: Participants (P): patients with PSD according to any diagnostic criteria. Intervention (I): CBT alone or CBT with antidepressants. Comparison (C): placebo or use of the same antidepressants with the CBT group. Outcomes (O): efficacy. Study design (S): RCTs with meta-analyzable data.

2.2. Search strategy

Both English (PubMed, Embase, and PsycINFO) and Chinese (China National Knowledge Infrastructure, WanFang and SinoMed) databases were independently searched from their inception date until April 12, 2017 by three investigators. The following search terms were used: (“stroke” OR “cerebrovascular accident” OR “brain vascular accident” OR “stroke, cerebral” OR “apoplexy”) AND (“depression” OR “depressive disorder” OR “melancholia” OR “unipolar depression”) AND (“cognitive behavior therapy” OR “cognitive therapy” OR “cognitive behavioral therapy” OR “cognitive psychotherapy” OR “cognitive behaviour therapy” OR “CBT”). The systematic search also included potential literature identified through Google Scholar. Further, the reference lists of retrieved reviews and RCTs were manually searched for trials that may have been previously missed.

2.3. Data extraction and outcome parameters

All-cause discontinuation and Intention-to-Treat (ITT) datasets regarding clinical outcomes were extracted independently by two investigators. Any inconsistencies during these procedures were reviewed and resolved by a discussion to reach a consensus.

The primary outcome measure was the change in the total scores of the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), Zung Self-Rating Depression Scale (SDS) (Zung, 1965), Hospital Anxiety and Depression Scale-Depression version (HADS-D) (Stern, 2014), or the Wakefield Self-assessment of Depression Inventory (WDI) (Snaith et al., 1971). The key secondary outcomes were the study-defined remission and response rates. Anxiety, neurological functional deficits and activities of daily living were also examined when available. Anxiety was measured with the Self-rating Anxiety Scale (SAS) (Zung, 1972); neurological functional deficit with the Neurological Function Deficit Scale (NFDS) (Chen, 1996) or the National Institutes of Health Stroke Scale (NIHSS) (Lyden et al., 2009); activities of daily living with the Barthel Index (Mahoney and Barthel, 1965), Activities of Daily Living Scale (ADL) (Dinnerstein et al., 1965) or Extended Activities of Daily Living (EADL) (das Nair et al., 2011); and cognitive functions with the Mini Mental State Examination (MMSE) (Pangman et al., 2000).

2.4. Assessment of study quality

The Cochrane Risk of Bias Tool (Higgins et al., 2003) and the Jadad scale (Jadad et al., 1996) were used to assess the risk of bias and quality of RCTs. From the Jadad scale (range: 0–5), a score ≥ 3 was rated as “high quality” and score < 3 as “low quality” (Jadad et al., 1996). The outcome measures of CBT were evaluated with the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system; the results were collapsed into very low, low, moderate, or high categories (or classes) (Atkins et al., 2004).

2.5. Statistical analyses

The Review Manager, Version 5.3 (http://www.cochrane.org) and R software, Version 3.2.3 were used to conduct the meta-analyses. The random effects model was performed in all cases. For continuous data, standardized mean difference (SMD) and their 95% confidence intervals (CIs) were used when the outcome was measured using different instruments. Otherwise, weighted mean difference (WMD) and their 95% CIs were applied. For dichotomous data, risk ratio (RR) and their 95% CIs were calculated using the Mantel-Haenszel test. Study heterogeneity was measured using I^2; I^2 values greater than 50% indicated heterogeneity (Higgins et al., 2003). Publication bias was examined with Funnel plots and Egger's test, as appropriate (Egger et al., 1997).

In order to identify moderators or mediators of the effect on outcome measures, nine subgroup analyses were conducted by contrasting the following factors: (1) Chinese studies vs. non-Chinese studies; (2) rater-masked studies vs. non-blinded studies; (3) studies with randomization details vs. those without randomization details; (4) studies using HAMD vs. studies using SDS vs. studies using other scales on depression; (5) treatment duration ≤ 8 weeks vs. duration > 8 weeks (median split); (6) mean number of CBT treatments ≤ 8 vs. treatments > 8 (median split); (7) inpatients vs. outpatients; (8) studies with a Jadad score ≥ 3 vs. studies with a Jadad score < 3. Furthermore, meta-regression analyses was performed to test the moderating effects of sample size, mean age, proportion of male participants, mean duration after the index stroke (weeks), mean CBT duration (weeks), mean number of CBT sessions, mean CBT duration in each session (hours), Jadad score of study quality, and baseline total HAMD score of the CBT group. Subgroup and meta-regression analyses were only performed when the heterogeneity was obvious ($I^2 \geq 50\%$) and the number of included studies was ≥ 10. All analyses were 2 tailed and the significance level was set at 0.05.

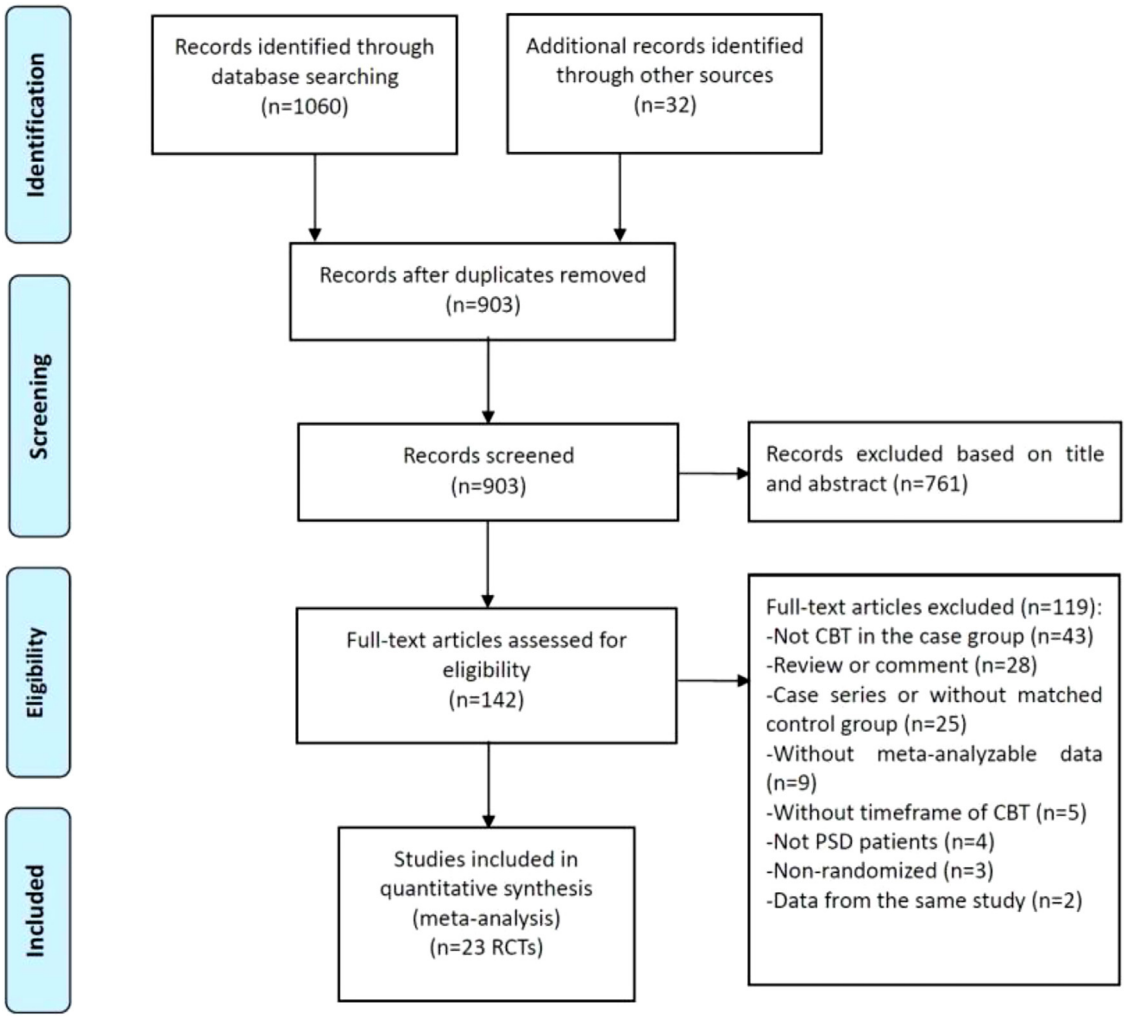

Fig. 1. PRISMA flow diagram.

3. Results

3.1. Selection of studies

Fig. 1 shows the process of study selection. The initial search produced 1092 results. After duplicates were removed, 903 titles and abstracts were reviewed, 142 articles were retrieved for full evaluation, and finally 23 RCTs which met the entry criteria were included in the meta-analysis.

3.2. Studies, participants, and treatment characteristics

Table 1 presents the characteristics of the included studies comprising 1,972 PSD subjects. PSD was assessed using the HAMD, Beck Depression Inventory (BDI), SDS, WDI, Chinese Classification of Mental Disorders (CCMD) and HADS-D. The mean age of participants ranged from 48.1 to 68.0 years (mean = 60.0, standard deviation = 5.6). The treatment duration of CBT ranged from 3 to 40 (mean = 9.5, median = 8) weeks. The number of CBT sessions ranged from 3 to 40 sessions (mean = 13.5, median = 14.3). Nine trials (Ge et al., 2016; Hao, 2014; He, 2010; Huang & Qiu, 2003; Lan, 2015; Li & Zhang, 2016; Lincoln & Flannaghan, 2003; Mei, 2012; Zhou & Wang, 2015) reported the duration after the index stroke, which varied widely from 2.0 to 292.2 weeks. Seven trials (Chen & Dai, 2015; Gao et al., 2017; He, 2010; Li et al., 2015; Mei, 2012; Wang & Yan, 2014; Yuan & Li, 2015) applied CBT alone in the intervention group and attention intervention or routine rehabilitation treatment in the control group. Fourteen trials (Fan and Wang, 2014; Ge et al., 2016; Hao, 2014; Hu et al., 2015; Huang and Qiu, 2003; Lan, 2015; Li and Zhang, 2016; Li and Zhao, 2009; Lin and Han, 2013; Lu, 2011; Tang et al., 2014; Wang, 2014; You, 2006; Zhou & Wang, 2015) used CBT in combination with antidepressants in the intervention group and antidepressants alone in the control group. In contrast, in the two trials conducted outside China (Kootker et al., 2017; Lincoln and Flannaghan, 2003) only a proportion of the subjects received antidepressants in both the CBT and placebo groups.

3.3. Evaluation quality of the studies and publication bias

The risk of publication bias is summarized in Supplemental Fig. 3. The method of randomization, particularly the random sequence, was unclear in 15 of the 23 studies. Only two studies provided information on the blindness of assessors. In most studies, outcome data were complete, missing data were explained adequately, and data collection tools were deemed valid and reliable. However, compliance with the intervention was only reported in 3 studies, with drop-out rates ranging from 5% to 15%. The Jadad scores ranged from 2 to 5, with a mean score of 2.7 (Table 1). Of the 23 RCTs, 39.1% (9/23) were rated as high quality studies, while 60.9% (14/23) were rated as low quality (Table 1). The results of GRADE assessment are shown in Supplemental Table 1.

The funnel plot of the effect of CBT on depression did not reveal any

Table 1
Summary of the characteristics of trials included in the meta-analysis.

Study ref.	Study (Country)	Sample size	Setting (inpatients/ outpatients); Blinding	Duration after the index stroke (week)	Measures on depression	Male (%)	Mean age (year)	Length of CBT and number of session	Antidepressant	Jadad score
27	Huang Y 2003 (China)	60	Both; Open-label	292.2	HAMD > 20	68.3	60.9	8 weeks (20)	Fluoxetine	2
13	Lincoln NB 2003 (UK) [a]	82	Both; Single blinding	11.5	BDI > 10 or WDI > 18	51.2	66.6	12 weeks (9.9)	Only for some patients	4
28	You 2006 (China)	58	Inpatients; Open-label	NR	HAMD > 9	56.9	59.4	12 weeks (NR)	Fluoxetine	2
29	Li L 2009 (China)	40	Inpatients; Open-label	NR	HAMD > 17	65.0	66.1	40 weeks (40)	Amitriptyline	2
22	He 2010 (China)	180	Inpatients; Open-label	4.0	HAMD > 18	55.6	55.6	4 weeks (8)	Not used	2
30	Lu 2011 (China) [b]	60	Inpatients; Open-label	NR	CCMD-3	41.1	61.3	8 weeks (8)	Fluoxetine	2
23	Mei 2012 (China)	160	Inpatients; Open-label	2.0	CCMD-2-R, SDS ≥ 50	71.3	60.0	4 weeks (8)	Not used	2
31	Lin LL 2013 (China)	40	Inpatients; Open-label	NR	HAMD	60.0	62.3	8 weeks (40)	Paroxetine	2
24	Wang JB 2014 (China)	60	Inpatients; Open-label	NR	HAMD > 18	58.3	59.0	8 weeks (3)	Not used	2
32	Wang 2014 (China)	110	Inpatients; Open-label	NR	HAMD ≥ 17	55.5	51.5	8 weeks (16)	Antidepressants	2
34	Fan WT 2014 (China)	44	Both; Open-label	NR	HAMD17 > 8	NA	NA	3 weeks (9)	Antidepressants	2
35	Hao 2014 (China)	119	Inpatients; Open-label	25.2	HAMD > 17	57.1	54.9	8 weeks (16)	Citalopram	2
33	Tang KH 2014 (China)	60	Outpatients; Open-label	NR	CCMD-3, HAMD > 17	58.3	62.6	6 weeks (6)	Citalopram	2
26	Yuan DW 2015 (China)	78	Inpatients; Open-label	NR	SDS > 52	62.8	64.5	12 weeks (12)	Not used	3
25	Chen XH 2015 (China)	88	Inpatients; Open-label	NR	SDS ≥ 50	65.9	68.0	2 weeks (NR)	Not used	3
21	Li AQ 2015 (China)	120	Inpatients; Open-label	NR	CCMD-3	60.8	56.0	8 weeks (NR)	Not used	3
37	Lan 2015 (China)	68	Inpatients; Open-label	33.9	CCMD-3	55.9	66.1	8 weeks (13.5)	Flupentixol and Melitracen	2
36	Zhou C 2015 (China)	75	Both; Double blinding	56.5	CCMD-3	56.0	65.5	8 weeks (16)	Duloxetine	4
38	Hu XF 2015 (China)	60	Inpatients; Open-label	NR	CCMD-3	65.0	52.3	8 weeks (8)	Citalopram	2
40	Ge DJ 2016 (China)	60	Inpatients; Open-label	5.0	HAMD ≥ 17	50.0	48.1	8 weeks (18)	Flupentixol and Melitracen	3
39	Li GF 2016 (China)	116	Inpatients; Open-label	14.0	HAMD > 17	58.6	53.2	8 weeks (24)	Citalopram	3
15	Gao et al. (2017) (China) [c]	173	Inpatients; Single blinding	NR	BDI > 10	51.8	66.0	12 weeks (24)	Not used	5
14	Kootker et al. (2017) (Netherlands)	61	Outpatients; Single blinding	NR	HADS-D > 7	62.3	61.0	16 weeks (15)	Only for some patients	5

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CCMD = Chinese Classification of Mental Disorders; HAMD = Hamilton Depression Rating Scale; HADS-D = Hospital Anxiety and Depression Scale-Depression version; NR = not reported; ref. = reference; SDS = Zung Self-Rating Depression Scale; UK = the United Kingdom; WDI = Wakefield Self-Assessment of Depression Inventory.

[a] CBT group and 'attention intervention' group were included for the meta-analysis.

[b] CBT + fluoxetine group and fluoxetine group were included for the meta-analysis.

[c] CBT group and psychological intervention group were included for the meta-analysis.

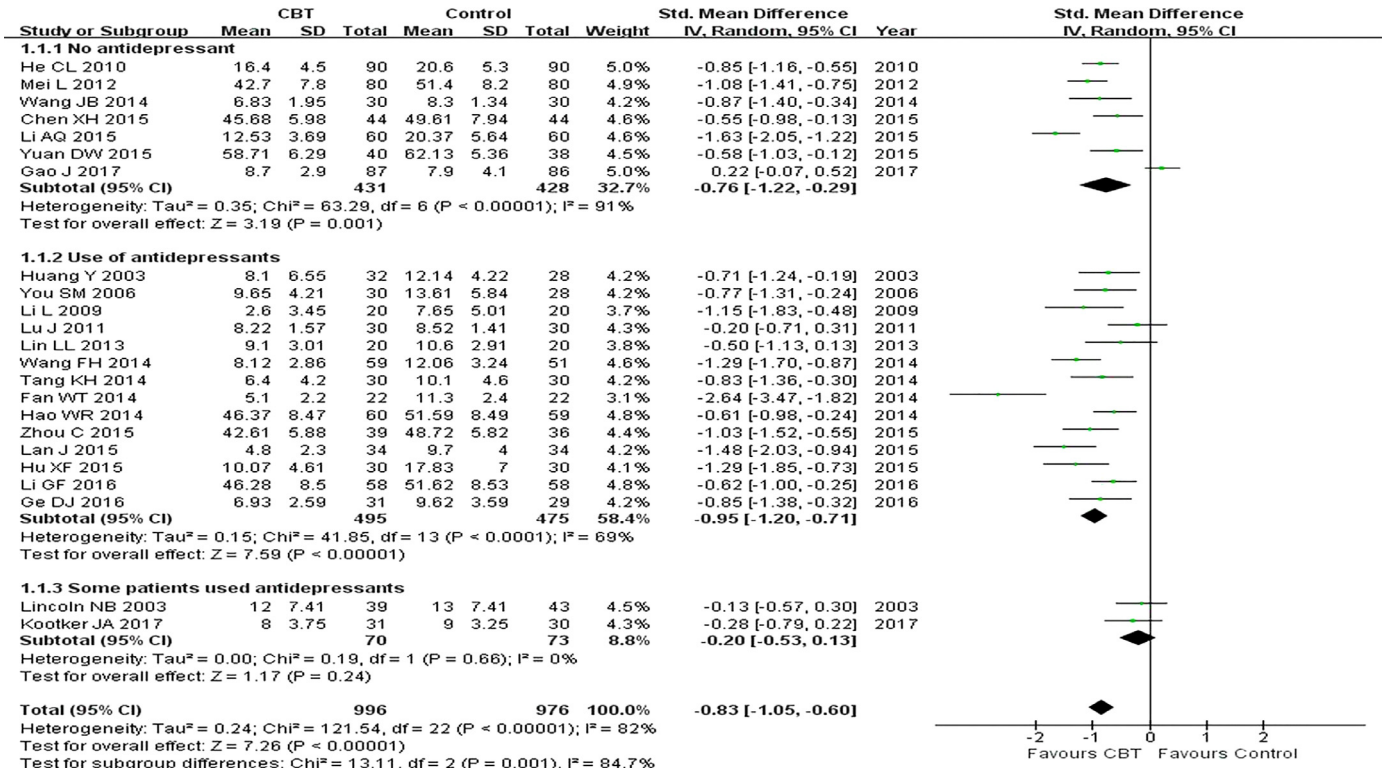

Fig. 2. Scale score of depression.

publication bias (Supplemental Figure 4). The Egger's regression test did not show statistically significant publication bias for the overall effect of CBT on PSD ($t = 1.98$, $P = 0.06$), anxiety ($t = 0.39$, $P = 0.69$), neurological functional deficit ($t = 1.80$, $P = 0.07$), and activities of daily living ($t = 1.09$, $P = 0.28$). In regard to the Egger's test, subgroup and sensitivity analyses were also conducted. In the subgroup analyses, Eggers' test did not reveal significant publication bias for the non-antidepressant ($t = 0.26$, $P = 0.79$) and the antidepressants groups ($t = 2.08$, $P = 0.06$), although publication bias in the antidepressants group showed a trend towards significance.

3.4. Effects of CBT on depression

Compared to the control groups, CBT showed a positive effect in PSD (23 arms, SMD = −0.83, 95% CI: −1.05 to −0.60, $P < 0.001$, $I^2 = 82\%$, Fig. 2). Both CBT alone (7 arms, SMD = −0.76, 95% CI: −1.22 to −0.29, $P = 0.001$, $I^2 = 91\%$) and CBT with antidepressants (14 arms, SMD = −0.95, 95% CI: −1.20 to −0.71, $P < 0.0001$, $I^2 = 69\%$) significantly improved depressive symptoms in PSD (Fig. 2). It should be noted, however, that significant heterogeneity existed in these analyses.

No significant improvement was found in the subgroup in which only a proportion of subjects received antidepressants. After removing four outlying studies (Fan and Wang, 2014; Gao et al., 2017; Li et al., 2015; Lincoln and Flannaghan, 2003), the overall results remained significant (19 arms, SMD = −0.81, 95% CI: −0.96 to −0.67, $P < 0.001$; $I^2 = 47\%$). CBT had significantly higher remission (6 arms, RR = 1.76, 95% CI: 1.37–2.25, $P < 0.00001$; $I^2 = 0\%$) and response rates (6 arms, RR = 1.41, 95% CI: 1.22–1.63, $P < 0.00001$; $I^2 = 35\%$) in PSD (Supplemental Figures 1 and 2). Only one study (Kootker et al., 2017) that combined CBT with goal-directed real-life activity training did not show any superiority over the control group.

3.5. Effects of CBT on other health aspects

Data on anxiety, neurological functional deficit, activities of daily living and cognitive function were pooled from studies with available data. Compared to controls, CBT was associated with improvement of anxiety, neurological functional deficit, and activities of daily living. Similar to the previous analyses, there was significant heterogeneity in these analyses (Table 2).

3.6. Subgroup and meta-regression analyses

Table 3 shows the subgroup analysis of improvement of depressive symptoms in PSD. Studies done in China, using open label design, using HAMD and SDS as the assessment scales, and having treatment duration ≤ 8 weeks showed greater improvement in each subgroup. In exploratory meta-regression analyses, significance was found between improvement of PSD with CBT and the following factors: sample size (Slope = 0.005, $P = 0.023$), mean age of subjects (Slope = 0.040, $P < 0.001$), proportion of male subjects (Slope = −0.031, $P < 0.001$), mean CBT duration (Slope = 0.020, $P = 0.019$), mean number of CBT sessions (Slope = 0.019, $P = 0.002$), Jadad score (Slope = 0.310, $P < 0.001$), CBT duration in each session (Slope = 0.604, $P = 0.002$) and baseline HAMD total scores in the CBT group (Slope = −0.083, $P < 0.001$). However, no significant relationship between CBT effects and the mean duration after stroke was found ($P > 0.05$), which could be due to the limited data available from only 9 trials.

4. Discussion

Reducing morbidity and mortality is a long term focus in the treatment of stroke (Broomfield et al., 2011). It is therefore important to address PSD as it is associated with increased morbidity, reduced quality of life and treatment burden in this population (Bays, 2001; Broomfield et al., 2011). To the best of our knowledge, this was the first meta-analysis of RCTs of CBT for PSD. The meta-analysis showed that

Table 2
CBT for post-stroke depression: effects on anxiety, neurological functional deficits, activities of daily living and cognitive function.

Variables		Endpoint symptomatic improvement				
		Subjects (arms)	SMDs or MDs[a] (95%CI)	I^2 (%)	P-value of overall effect	P-value of subgroup difference
Anxiety	Overall	403 (5)	−0.49 (−0.79, −0.19)	55	0.001	0.64
	No antidepressant	88 (1)	−0.49 (−0.92, −0.07)	NA	0.02	
	Use of antidepressants	254 (3)	−0.58 (−1.09, −0.06)	74	0.03	
	Some patients received antidepressants	61 (1)	−0.25 (−1.09, −0.06)	NA	0.34	
Neurological function deficit	Overall	382 (5)	−1.22 (−1.80, −0.64)	84	<0.001	0.07
	No antidepressant	160 (1)	−0.67 (−0.99, −0.35)	NA	<0.001	
	Use of antidepressants	222 (4)	−1.38 (−2.07, −0.69)	81	<0.001	
Activities of daily living	Overall	753 (7)	0.78 (0.15, 1.41)	94	0.01	0.15
	No antidepressant	551 (4)	0.68 (−0.14, 1.51)	95	0.10	
	Use of antidepressants	120 (2)	1.42 (−0.41, 3.24)	95	0.13	
	Some patients received antidepressants	82 (1)	0.00 (−0.43, 0.43)	NA	1.00	
Cognitive function	Overall	283 (2)	−2.67 (−7.04, 1.70)	95	0.28	<0.001
	No antidepressant	173 (1)	−0.40 (−1.98, 1.18)	NA	0.62	
	Use of antidepressants	110 (1)	−0.75 (−0.95, −0.55)	NA	<0.001	

CBT = cognitive behavioral therapy; SMDs = standardized mean differences; MDs = mean differences; NA = not applicable.
[a] SMD was calculated in anxiety, activities of daily living and neurological functional deficits due to the different scales used; MD was calculated for cognitive function because the two studies used the same scale

both CBT alone and CBT combined with antidepressants significantly improved depressive symptoms, response and remission rates in PSD. However, given the potential bias, significant heterogeneity and the low quality across the majority of the studies, these findings are not conclusive and should be considered as preliminary.

The basic principle of CBT is that patients' behavior can be changed, and the nature of an individual's problems can be conceptualized within a behavioral frame of reference (Laidlaw et al., 2004). As PSD is a heterogeneous disorder (Kneebone and Dunmore, 2000), CBT requires customized adaptation for PSD given that no single model of CBT is always suitable. For example, when applying CBT for older and frail patients, the therapist needs to be creative in individualizing therapeutic interventions (Grant and Casey, 1995). Not surprisingly, the treatment duration and the number of CBT sessions varied widely across the included studies, which thus limits its generalizability.

The effect of CBT on anxiety has been consistently reported (Hofmann and Smits, 2008; McMain et al., 2015). This meta-analysis found that both CBT alone and CBT combined with antidepressants significantly improved anxiety. Further, improvement in psychiatric symptoms is also associated with an improvement in motor symptoms and quality of life (Berardelli et al., 2015). This study found overall improvement in neurological functional deficits and activities of daily living in the CBT group, which is consistent with previous studies (Ricciardi and Edwards, 2014).

Sociocultural factors have a major impact on the clinical presentation of depression (Chen et al., 2015; Jeon et al., 2014). The adaptation of CBT for PSD varies according to the given socio-cultural context (Rathod et al., 2013). This meta-analysis included 21 studies from China and 2 studies from the UK and Netherlands respectively. Subgroup analyses have shown significant improvement in PSD in Chinese studies, but not in Western studies. Several factors could explain such discrepancy. Many aspects of CBT appear to match well with Chinese

Table 3
Subgroup and sensitivity analyses of CBT for post-stroke depression stratified by previously defined study characteristics.

Variables	Endpoint symptomatic improvement				
	Subjects (arms)	SMDs (95%CI)	I^2 (%)	*P*-value of overall effect	*P*-value of subgroup difference
1. Chinese studies	1829 (21)	−0.89 (−1.12, −0.66)	82	<0.001	**<0.001**
Non-Chinese studies	143 (2)	−0.20 (−0.53, 0.13)	0	0.24	
2. Rater masked	391 (4)	−0.29 (−0.82, 0.24)	84	0.29	**0.02**
Open label	1581 (19)	−0.94 (−1.14, −0.74)	70	<0.001	
3. Has randomization details	744 (8)	−0.77 (−1.30, −0.23)	92	0.005	0.68
No randomization details	1228 (15)	−0.88 (−1.05, −0.72)	46	<0.001	
4. HAMD	1193 (15)	−0.96 (−1.30, −0.63)	86	<0.001	**0.003**
SDS	636 (6)	−0.75 (−0.95, −0.55)	33	<0.001	
Others (BDI/HADS-D)	143 (2)	−0.20 (−0.53, 0.13)	0	0.24	
5. Treatment duration ≤ 8 weeks [a]	1480 (17)	−0.97 (−1.18, −0.76)	72	<0.001	**0.01**
Treatment duration > 8 weeks	492 (6)	−0.40 (−0.80, −0.01)	82	0.05	
6. Number of CBT sessions ≤ 8 [a]	580 (6)	−0.86 (−1.12, −0.60)	52	<0.001	0.73
Number of CBT sessions > 8	1126 (14)	−0.79 (−1.11, −0.47)	85	<0.001	
7. Inpatients	1590 (17)	−0.82 (−1.07, −0.57)	82	<0.001	0.37
Outpatients	121 (2)	−0.55 (−1.09, −0.01)	54	0.05	
8. Jadad score ≥ 3	853 (9)	−0.60 (−0.99, −0.21)	87	0.003	0.11
Jadad score < 3	1119 (14)	−0.97 (−1.20, −0.75)	68	<0.001	

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; HADS-D = Hospital Anxiety and Depression Scale-Depression version; HAMD = Hamilton Depression Rating Scale; SDS = Zung Self-Rating Depression Scale; SMDs = standardized mean differences.
[a] Using the median split of the number.

cultural values, such as Confucianism, Taoism, and Buddhism (Guo and Hanley, 2015). Further, concomitant use of antidepressants varied; in the two Western studies, only a proportion of subjects used antidepressants in the CBT and control groups, while in two-thirds of the Chinese studies, all subjects in both groups received antidepressants. Moreover, the quality of the Chinese studies was assessed to be lower than that of the Western studies.

Effects of CBT were significantly associated with the assessment measures. Studies using the HAMD observed greater therapeutic effects than those using the SDS, while studies using BDI and HADS-D had no significant results. BDI and HADS-D contain items that overlap with the effects of stroke, such as psychomotor slowing and apathy, which is likely to reduce their sensitivity to depressive symptoms in PSD (Dahm et al., 2013; Whelan-Goodinson et al., 2009). In addition, the cognitive impairment and the severity of depressive symptoms in the acute stage of stroke may affect the sensitivity of certain screening tools to depressive symptoms (Lees et al., 2014).

The effect size in studies with treatment duration of ≤ 8 weeks was significantly higher than that of those studies with treatment >8 weeks. This trend was also confirmed in the meta-regression analysis on treatment duration and the mean number of CBT sessions. Factors that influence the treatment duration of CBT include the severity of depressive symptoms, response time, stress level, and family and social support (Feng et al., 2012).

The results of this meta-analysis need to be interpreted with caution due to several limitations. First, there was significant heterogeneity in the results, even though the random effects model and standard mean differences were used. Second, 60.9% (14/23) of the RCTs were rated as of low quality studies. In addition, the majority of the studies (21/23) were conducted in China, which limits the generalizability of the findings. Furthermore, most studies excluded patients who had visual, auditory and/or severe cognitive deficits or other severe comorbidities. Fourth, the length of treatment ranged from 3 to 40 weeks, so the long-term effect of CBT could not be meaningfully examined. Finally, although spontaneous remission in PSD is possible, the use of control group would have addressed potential bias.

5. Conclusions

This meta-analysis found that both CBT alone and adjunctive CBT with antidepressants appear efficacious in improving depressive symptoms in PSD. However, due to the limitations of the included studies the evidence for CBT remains inconclusive and future high-quality RCTs are needed.

Author Statement

Conflict of interest

The authors declare that they have no conflicts of interest concerning this paper.

Role of funding

This study was funded by the Beijing Brain Research Institute (Z161100000216131), and the Ministry of Science and Technology of China (2015BAI13B03; 2016YFC1307205).

Contributors

Study Design: Shi-Bin Wang, Yuan-Yuan Wang, Qinge Zhang, Yu-Tao Xiang. Analysis and interpretation of data: Shi-Bin Wang, Yuan-Yuan Wang, Shuo-Lin Wu, Qinge Zhang. Drafting of the manuscript: Shi-Bin Wang, Liang Chen, Fu-Jun Jia, Yu-Tao Xiang. Critical revision of the manuscript: Chee H. Ng, Gabor S. Ungvari, Chun-Xue Wang. Approval of the final version for publication: all the authors.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.04.011.

References

Atkins, D., Best, D., Briss, P.A., Eccles, M., Falck-Ytter, Y., Flottorp, S., Guyatt, G.H., Harbour, R.T., Haugh, M.C., Henry, D., Hill, S., Jaeschke, R., Leng, G., Liberati, A., Magrini, N., Mason, J., Middleton, P., Mrukowicz, J., O'Connell, D., Oxman, A.D., Phillips, B., Schunemann, H.J., Edejer, T., Varonen, H., Vist, G.E., Williams Jr., J.W., Zaza, S., 2004. Grading quality of evidence and strength of recommendations. BMJ 328, 1490.

Bays, C.L., 2001. Quality of life of stroke survivors: a research synthesis. J. Neurosci. Nurs. 33, 310–316.

Berardelli, I., Pasquini, M., Roselli, V., Biondi, M., Berardelli, A., Fabbrini, G., 2015. Cognitive behavioral therapy in movement disorders: a review. Mov. Disord. Clin. Pract. 2, 107–115.

Broomfield, N.M., Laidlaw, K., Hickabottom, E., Murray, M.F., Pendrey, R., Whittick, J.E., Gillespie, D.C., 2011. Post-stroke depression: the case for augmented, individually tailored cognitive behavioural therapy. Clin. Psychol. Psychother. 18, 202–217.

Cadilhac, D.A., Andrew, N.E., Lannin, N.A., Middleton, S., Levi, C.R., Dewey, H.M., Grabsch, B., Faux, S., Hill, K., Grimley, R., Wong, A., Sabet, A., Butler, E., Bladin, C.F., Bates, T.R., Groot, P., Castley, H., Donnan, G.A., Anderson, C.S., 2017. Quality of acute care and long-term quality of life and survival: the australian stroke clinical registry. Stroke 48, 1026–1032.

Chen, J.A., Hung, G.C., Parkin, S., Fava, M., Yeung, A.S., 2015. Illness beliefs of Chinese American immigrants with major depressive disorder in a primary care setting. Asian J. Psychiatr. 13, 16–22.

Chen, Q.T., 1996. Cerebral apoplexy patients clinical nerve function deficit score criteria. Chin. J. Neurol. 29, 381–383.

Chen, X.H., Dai, M.X., 2015. Cognitive behavioral nursing intervention on prognosis of post-stroke depression. J. Tradit. Chin. Med. Manage. 23, 159–160.

Dahm, J., Wong, D., Ponsford, J., 2013. Validity of the depression anxiety stress scales in assessing depression and anxiety following traumatic brain injury. J. Affect. Disord. 151, 392–396.

DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., O'Reardon, J.P., Lovett, M.L., Gladis, M.M., Brown, L.L., Gallop, R., 2005. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch. Gen. Psychiatry 62, 409–416.

Dinnerstein, A.J., Lowenthal, M., Dexter, M., 1965. Evaluation of a rating scale of ability in activities of daily living. Arch. Phys. Med. Rehabil. 46, 579–584.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Fan, W.T., Wang, Q., 2014. Clinical research of xingnaoJieyu capsule combined with cognitive behavior therapy in treating poststroke depression. China J. Chin. Med. 29, 101–105.

Feng, C.Y., Chu, H., Chen, C.H., Chang, Y.S., Chen, T.H., Chou, Y.H., Chang, Y.C., Chou, K.R., 2012. The effect of cognitive behavioral group therapy for depression: a meta-analysis 2000-2010. Worldviews Evid. Based Nurs. 9, 2–17.

Gao, J., Lin, M., Zhao, J., Bi, S., Ni, Z., Shang, X., 2017. Different interventions for post-ischaemic stroke depression in different time periods: a single-blind randomized controlled trial with stratification by time after stroke. Clin. Rehabil. 31, 71–81.

Ge, D.J., Wu, L.Y., Sun, S.F., Shang, L., Yang, Q.J., Yang, X.R., Zhao, Q.X., 2016. Deanxit combined with cognitive behavioral therapy in treating 31 cases of post-stroke depression. Rehabil. Med. 26, 38–41.

Grant, R.W., Casey, D.A., 1995. Adapting Cognitive Behavioral Therapy for the Frail Elderly. Int. Psychogeriatr. 7, 561–571.

Guo, F., Hanley, T., 2015. Adapting cognitive behavioral therapy to meet the needs of Chinese clients: opportunities and challenges. Psych J. 4, 55–65.

Hackam, D.G., Mrkobrada, M., 2012. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. Neurology 79, 1862–1865.

Hackett, M.L., Anderson, C.S., House, A., Xia, J., 2008. Interventions for treating depression after stroke. Cochrane Database Syst. Rev CD003437.

Hackett, M.L., Anderson, C.S., House, A.O., 2005. Management of depression after stroke: a systematic review of pharmacological therapies. Stroke 36, 1098–1103.

Hackett, M.L., Pickles, K., 2014. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int. J. Stroke 9, 1017–1025.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hao, W.R., 2014. Citalopram combined with cognitive behavior intervention on post-stroke depression, anxiety and quality of life. Chin. J. Pract. Nerv. Dis. 17, 109–110.

He, C.L., 2010. Influence of psychological nursing intervention on post-stroke depression.

China Mod. Dr. 48, 68–71.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
Hofmann, S.G., Smits, J.A., 2008. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatry 69, 621–632.
House, A., Dennis, M., Mogridge, L., Warlow, C., Hawton, K., Jones, L., 1991. Mood disorders in the year after first stroke. Br. J. Psychiatry 158, 83–92.
Hu, X.F., Pan, X.M., Zhang, Y., 2015. Comparative study of effects of three treatment methods for post-stroke depression. Med. J. Chin. People´s Health 27, 13–34.
Huang, Y., Qiu, X.L., 2003. Study on the therapeutic effects of cognitive and behavioral therapies on post-stroke depression. Int. Med. Health Guidance News 9, 12–13.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17, 1–12.
Jeon, H.J., Walker, R.S., Inamori, A., Hong, J.P., Cho, M.J., Baer, L., Clain, A., Fava, M., Mischoulon, D., 2014. Differences in depressive symptoms between Korean and American outpatients with major depressive disorder. Int. Clin. Psychopharmacol. 29, 150–156.
Kneebone II, , Dunmore, E., 2000. Psychological management of post-stroke depression. Br. J. Clin. Psychol. 39 (Pt 1), 53–65.
Kootker, J.A., Rasquin, S.M., Lem, F.C., van Heugten, C.M., Fasotti, L., Geurts, A.C., 2017. Augmented cognitive behavioral therapy for poststroke depressive symptoms: a randomized controlled trial. Arch. Phys. Med. Rehabil. 98, 687–694.
Kootker, J.A., Rasquin, S.M., Smits, P., Geurts, A.C., van Heugten, C.M., Fasotti, L., 2015. An augmented cognitive behavioural therapy for treating post-stroke depression: description of a treatment protocol. Clin. Rehabil. 29, 833–843.
Laidlaw, K., Thompson, L.W., Gallagher-Thompson, D., 2004. Comprehensive conceptualization of cognitive behaviour therapy for late life depression. Behav. Cognit. Psychother. 32, 389–399.
Lan, J., 2015. Flupentixol melitracen combined with cognitive behavior therapy in the treatment of post-stroke depression. For All Health 9, 131–132.
Lees, R., Stott, D.J., Quinn, T.J., Broomfield, N.M., 2014. Feasibility and diagnostic accuracy of early mood screening to diagnose persisting clinical depression/anxiety disorder after stroke. Cerebrovasc. Dis. 37, 323–329.
Li, A.Q., Zhu, Z.M., Yin, Y.H., Wang, H.J., 2015. Cognitive Behavioral Intervention on the rehabilitation effect of patients with post-stroke depression. Chin. J. Geriatr. Care 13, 125–126.
Li, G.F., Zhang, Z.L., 2016. Analysis of citalopram combined with cognitive behavior intervention on post-stroke depression, anxiety, and quality of life using 58 patients. Chin. J. Pract. Nerv. Dis. 19, 110–111.
Li, L., Zhao, M.F., 2009. Cognitive behavioral therapy for patients with post-stroke depression in the restoration process. J. Bengbu Med. Coll. 34, 214–215.
Lin, L.L., Han, Y.E., 2013. Cognitive behavior therapy combined with paroxetine on post-stroke depression and neurological rehabilitation. Chin. J. Clin. Res. 26, 1329–1330.
Lincoln, N.B., Flannaghan, T., 2003. Cognitive behavioral psychotherapy for depression following stroke: a randomized controlled trial. Stroke 34, 111–115.
Lu, J., 2011. Comparative study of three kinds of treatment on post-stroke depression. J. Community Med. 9, 29–30.
Lyden, P., Raman, R., Liu, L., Emr, M., Warren, M., Marler, J., 2009. National institutes of health stroke scale certification is reliable across multiple venues. Stroke 40, 2507–2511.
Mahoney, F.I., Barthel, D.W., 1965. Functional evaluation: the Barthel index. Md. State Med. J. 14, 61–65.
McMain, S., Newman, M.G., Segal, Z.V., DeRubeis, R.J., 2015. Cognitive behavioral therapy: current status and future research directions. Psychother. Res. 25, 321–329.
Mead, G.E., Hsieh, C.F., Lee, R., Kutlubaev, M.A., Claxton, A., Hankey, G.J., Hackett, M.L., 2012. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst. Rev. 11 Cd009286.
Mei, L., 2012. Effect analysis of cognitive behavior therapy on post-stroke depression and neurological rehabilitation. Mod. J. Integr. Tradit. Chin. West. Med. 21, 600–601.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 151, 264–269 w264.
Nair, das, R., Moreton, J., B., Lincoln, N.B., 2011. Rasch analysis of the Nottingham extended activities of daily living scale. J. Rehabil. Med. 43, 944–950.
Pangman, V.C., Sloan, J., Guse, L., 2000. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. Appl. Nurs. Res. 13, 209–213.
Rathod, S., Phiri, P., Harris, S., Underwood, C., Thagadur, M., Padmanabi, U., Kingdon, D., 2013. Cognitive behaviour therapy for psychosis can be adapted for minority ethnic groups: a randomised controlled trial. Schizoph. Res. 143, 319–326.
Ricciardi, L., Edwards, M.J., 2014. Treatment of functional (psychogenic) movement disorders. Neurotherapeutics 11, 201–207.
Robinson, R.G., Jorge, R.E., 2016. Post-stroke depression: a review. Am. J. Psychiatry 173, 221–231.
Snaith, R.P., Ahmed, S.N., Mehta, S., Hamilton, M., 1971. Assessment of the severity of primary depressive illness. Wakef. Self-assess. Depression Inventory Psychol. Med. 1, 143–149.
Stern, A.F., 2014. The hospital anxiety and depression scale. Occup. Med. (Lond.) 64, 393–394.
Swartz, R.H., Bayley, M., Lanctot, K.L., Murray, B.J., Cayley, M.L., Lien, K., Sicard, M.N., Thorpe, K.E., Dowlatshahi, D., Mandzia, J.L., Casaubon, L.K., Saposnik, G., Perez, Y., Sahlas, D.J., Herrmann, N., 2016. Post-stroke depression, obstructive sleep apnea, and cognitive impairment: Rationale for, and barriers to, routine screening. Int. J. Stroke 11, 509–518.
Tang, K.H., Yan, Y., Li, X., 2014. The effects of escitalopram combined with cognitive therapy on post-stroke depression and nerve function. China J. Health Psychol. 22, 1775–1777.
van Mierlo, M.L., van Heugten, C.M., Post, M.W., Hajos, T.R., Kappelle, L.J., Visser-Meily, J.M., 2016. Quality of life during the first two years post stroke: the restore4stroke cohort study. Cerebrovasc. Dis. 41, 19–26.
Wang, F.H., 2014. Curative effect of psychotherapy intervention for improving depression and Cognitive impairment following stroke. Chin. J. Clin. 8, 407–410.
Wang, J.B., Yan, W.J., 2014. Applied cognitive-behavior therapy in rehabilitation nursing in stroke patients with depression. Today Nurse 31–32.
Whelan-Goodinson, R., Ponsford, J., Schonberger, M., 2009. Validity of the Hospital Anxiety and Depression Scale to assess depression and anxiety following traumatic brain injury as compared with the Structured Clinical Interview for DSM-IV. J. Affect. Disord. 114, 94–102.
You, S.M., 2006. Treatment of depression after cerebral stroke. Mod. Diagn. Treat. 17, 274–275.
Yuan, D.W., Li, J., 2015. Effect study of cognitive behavioral intervention on depression status and quality of life in patients with stroke. J. Neurosci. Ment. Health 15, 243–246.
Zhou, C., Wang, P., 2015. Cognitive behavior therapy combined with duloxetine effect analysis on treatment of post-stroke depression. J Nantong Univ. (Med. Sci.) 35, 592–593.
Zung, W.W., 1965. A self-rating depression scale. Arch. Gen. Psychiatry 12, 63–70.
Zung, W.W., 1972. The depression status inventory: an adjunct to the self-rating depression scale. J. Clin. Psychol. 28, 539–543.