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The Effectiveness of Cognitive Behavioral Therapy for People with Depression Following Stroke: A Systematic Review and Meta-Analysis

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Abstract

Post-stroke depression (PSD) is a common psychiatric manifestation of stroke, which has a devastating impact on survivors' quality of life with an increasing burden on caregivers and the public medical system. Even so, no meta-analysis on specific psychotherapeutic treatment has been conducted. How effective is cognitive behavioral therapy (CBT) in reducing depressive symptoms in randomized-controlled trials (RCTs) targeting community-dwelling stroke survivors with PSD? Through systematic procedures of screening and data extraction, four RCTs were synthesized for meta-analysis (N= 270) on effect size estimates. Overall, CBT groups showed significant improvement in depression compared with controls. Methodological quality, intensity of CBT, and duration of post-treatment follow-up proved critical to treatment effects. Despite the potential threat of external validity, this paper had reviewed their content comprehensively with the implication of facilitating public understanding, research, and service development of PSD using CBT. To fill the knowledge gap, standardized protocol and further subgroup analyses are necessary.

Keywords: Cognitive Behavioral Therapy, Meta-Analysis, Neuropsychology, Poststroke Depression, Psychotherapy

Introduction

Stroke is one of the most serious illnesses by universal consensus because of its high mortality and disability rate (House et al., 2001; Whyte & Mulsant, 2002). From the statistical report released by the World Health Organization (2017), stroke, as the 2nd leading cause of death worldwide has killed 6.2 million people in 2011. Referring to the Hospital Authority (2013), over 3,660 people suffered from stroke and had to be hospitalized and about 30% of them died in 2012. On average, over 3,000 people in Hong Kong die of stroke every year, as reported by the Department of Health (2014). With the advancement of techniques in neuroimaging and thrombolysis, the mortality rate of stroke has been under control (Pantoni et al., 2013). It paradoxically leads to higher accumulative comorbidity, as most stroke survivors have different degrees of motor-sensory dysfunctions, slurred speech, and psychological impediments. Overall, 30% to 61% of the survivors worldwide suffer from post-stroke depression (PSD) within 1 year after the onset of stroke, regardless of demographical factors (Dafer, Shareef &

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Sharma, 2008; Hackett et al., 2009; Robinson, 1997).

What Is Post-Stroke Depression?

Post-Stroke depression (PSD) is defined as the persistent negative mood changes triggered by cerebrovascular accident (Paolucci, 2008). According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; APA, 2013), people who are clinically diagnosed with a major depressive disorder must meet 5 or more symptoms: depressed mood, diminished interest or pleasure (at least 1 of the first 2 criteria), significant weight loss or weight gain, insomnia or hypersomnia, psychomotor disorder, fatigue, excessive guilt or sense of worthlessness, difficulty concentrating or making decision, and suicidal ideation, for the duration of not less than 2 weeks.

In general, clinicians roughly divided those with PSD into two subtypes: early onset (PSD develops within 3 months or less post-stroke) and late onset (3 months or more post-stroke), which were characterized by psychosomatic features of depression (e.g., poor sleep and appetite, low pain tolerance or other physiological discomfort), persistent sadness and hopelessness, maladaptation in role changes in a family, and loss of interest or lack of motivation to engage in previously liked hobbies and social lives (Coster et al., 2005). Stroke survivors were at stake for PSD in the first two years, with the peak between 3 and 6 months (Paolucci, 2008). Besides, researchers have identified several risk factors for PSD, including female, old age, home-dwellers without social support, unemployment, inability to convey barrier-free communication, and high severity of stroke, as well as history of depression and other physical illness (De Ryck et al., 2013; Thomas & Lincoln, 2006).

Why Do We Need to Study PSD and Its Psychological Treatment Seriously?

Depressive mood is a common psychiatric manifestation of stroke (Go et al., 2013, Paolucci, 2008). Defer and colleagues (2008) evaluated the frequency of occurrence of psychiatric problems and found that depression (> 60%) is about 2 times more likely to occur in the survivors compared with other symptoms, such as irritability, poor appetite, aggression, apathy, and anxiety. Clinicians also concerned about the slight increase in the number of people getting from stroke at a younger age (Griffiths & Sturm, 2011). Lokk and Delbari (2010) compared a set of psychological markers by two age groups using 60 as a cut-off and found that young stroke survivors were less prone to cognitive deterioration, somatic problems, anxiety, and hypochondria, but significantly more severe in depression.

The negative effects of PSD on multifaceted layers of the society raise additional concerns. It has caused an increasing burden on public medical service (e.g., length of stay in the hospital, frequent readmission, shortage of manpower), negatively affected caregivers' quality of life, and increased risk of second stroke (Go et al., 2013; Paolucci, 2008; Robinson, 2003). Yuen and colleagues (2012) found that PSD, when developed in an acute phase, increases the risk of recurrent stroke by 49% in 1 year and that the increased risk had not been reduced by the treatment of antidepressants in the Chinese population.

This study highlighted not only the negative effects of PSD on the health of stroke sufferers but also the limitation of treatment effect on PSD using anti-depressants alone.

Although antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are considered the first-line treatment for PSD, psychologists were interested in the proper application of the non-pharmacological method as an alternative or supplementary way to reach optimal treatment effect (Finkenzeller et al., 2009).

Cognitive Behavioral Therapy in PSD

The phenomenon of PSD worsening stroke survivors' and their stakeholders' physical and psychological health provoked practitioners' thought on the treatment effect of Cognitive Behavioral Therapy (CBT). According to Beck and Beck (2011), the rationale of CBT is that human emotion is the product of how people think and believe. Therapists help clients identify physiological warning signs, irrational beliefs, emotions, and outward behaviors (Beck & Beck, 2011). Subsequently, this therapeutic process may loosen their internal rules and regulations by self-challenging and reconstructing positive adaptive coping strategies on here-and-now basis (Beck & Beck, 2011). Once the core part of cognition is strengthened, people become capable of dealing with maladaptive behavior and negative emotion faced in everyday life. Psychologists believe that CBT can help relieve the symptoms of depression among stroke sufferers and in turn facilitate their motivation to self-help, instill hope, and restore functionality to improve the quality of life (Finkenzeller et al., 2009; Lincoln & Flannagan, 2003; Robinson, 2003).

Despite the severity of the PSD, evidence-based knowledge of the use of CBT in the treatment of PSD is ironically sparse. Broomfield and colleagues (2011) reviewed the treatment effect of CBT for PSD and found only three studies that utilized different research designs: one pilot study of control trial, one RCT, and one single-subject quasi-experiment in AB design. The question of whether the effect of CBT is more superior compared with that of controls in reducing PSD remains inconclusive (Broomfield et al., 2011; Hackett et al., 2008; Lincoln & Flannagan, 2003; Lincoln et al., 1997). In contrast, CBT has been widely used to treat health problems induced by depression (Beck & Beck, 2011; Sudak, 2012), and, through a broad consensus, it has proved to be effective in treating depression in clinical neurosciences, such as Parkinson's disease (Dobkin et al., 2011), traumatic brain injury (Khan-Bourne & Brown, 2003), brain tumor (Poggi et al., 2009), and post-neurosurgical injury (Waldron et al., 2013).

Objectives

The study aimed to fill the knowledge gap in the application of CBT to PSD by systematically evaluating research design and meta-analyzing data of identified individual studies using PICOs (stands for "population", "intervention", "comparison", "outcome", and "setting or study type"). The question is: In community-dwelling stroke survivors with post-stroke depression (PSD), how effective is Cognitive Behavioral Therapy (CBT) compared with Controls in reducing depressive symptoms, as assessed by post-treatment Beck Depression Inventory (BDI) or Hamilton Rating Scale for Depression (HAM-D) scores in randomized-controlled trials (RCTs)?

Methodology

Protocol

A deliberate protocol was developed to frame PICOs question, identify and screen relevant literature, assess the quality of selected studies, extract and summarize the data, and interpret the results according to the recommendations of the Cochrane Collaboration. The review fully complied with the reporting system of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

Eligibility Criteria

The studies in this systematic review had to match with the stated PICOs with specific criteria, including 1) participants with depressive symptoms after stroke clinically diagnosed as major depressive disorder or depression by commonly used psychiatric diagnostic tool (e.g., DSM-IV or ICD-10) or depressive mood identified using standardized and valid tool (e.g., Ham-D or BDI); 2) randomized control trials (RCTs) as the research design; 3) cognitive behavioral therapy or its branches of approach that involved elements of CBT as a major intervention; 4) having a comparison between CBT and Control, with or without conventional care, or psychopharmacological treatment if equally delivered to both groups, and 5) evaluated by validated clinical outcome measures such as BDI and HAM-D.

Information Sources and Search

The researcher (author) searched for RCTs that evaluated the treatment effects of CBT in people with PSD published in all languages since 1970 (see Figure 1). He used common online databases, including Cochrane (Cochrane Central Register of Controlled Trials), Pub-Med, EBSCO, Proquest, PsycINFO, EMBASE, Google Scholar, and Yahoo Engine, to find relevant publications for further screening. References of the selected articles were also examined by hand to minimize the chance of missing. This process lasted from the 2017 winter to the 2018 spring.

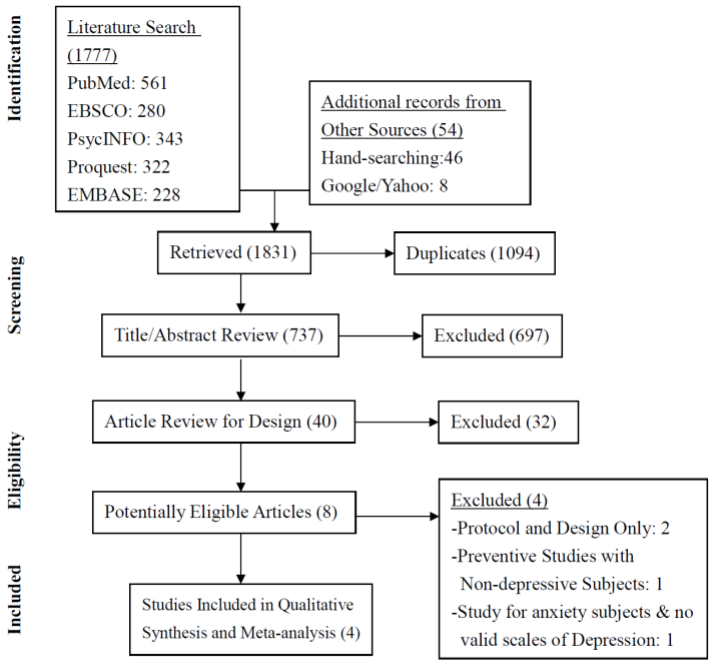

FIGURE 1. Flow diagram of PRISMA

Study Selection

The researcher applied the above-mentioned search method to identify the potential studies and then integrated them into an Excel database. One postgraduate student in psychology with research experience in conducting systematic review was invited as an assistant to work together on initial screening of the titles and abstracts of the articles. Then, two persons independently screened for eligible articles in accordance with eligibility criteria and made a final decision for the inclusion of studies.

Screening Process

The assistant and researcher screened the abstract from "Abstract review"

independently using a predesigned form in Excel file, with preliminary remarks on stroke, depression or depressive or mood- related, type of therapy (CBT), RCT, and included outcome measures of depression. Before initiating the data extraction process, additional screening was conducted to determine whether the studies included CBT techniques and complied with standard CBT-relevant guidelines.

Critically, the inclusion criteria of CBT is relatively ill-defined, as many psychotherapies that are named differently (e.g., Cognitive Therapy, Rationale-Emotive Behavioral Therapy, Dialectic Behavioral Therapy… etc.) fall under the umbrella of CBT. Some studies might apply the components of CBT but only denoted the intervention as a general rehabilitation program in a subtle way. The review, by clinical judgment, selected those that employed cognitive and behavioral components as the key concept for the treatment.

Data Extraction and Data Items

For selected studies, the assistant and researcher conducted qualitative and quantitative data extraction. They independently used piloted standard forms to record details and statistical findings prior to discussing for discrepancies and combining data. The researcher attempted to contact 4 RCT authors for further information of their research methodologies, CBT administration, and findings, but the response rate was low (25%; invalid email = 1; non-replied = 2; replied = 1).

The details of research methods and designs were explored, including country or setting of the studies, exclusion criteria, participants' demographic characteristics and details of treatment (CBT) vs. control group, outcome measures, and statistical findings (see Table 1). The details of the CBT quality in terms of the type of the treatment and its components, intensity (time, frequency, total session, and follow- up) of co-therapy, and other backgrounds of CBT administration are summarized in Table 2.

Risk of Bias in Individual Studies

Methodological quality of RCTs was evaluated using a scale comprising 8 parameters (see Table 3). Two raters, namely V and KC, independently evaluated the scale and calculated the total quality scores by cumulatively adding 1 score for each parameter that was rated "adequate". The ratings ranged from 0 to 8, with scores 0-3 = low, 4-6 = moderate, and 7-8 = high methodological quality, respectively. Using the Statistical Package for Social Sciences (SPSS) version 22.0, Cohen's Kappa (κ) was applied to review the inter-rater consistency. Landis and Koch (1977) provided a set of benchmarks for the interpretation of Kappa agreement: 0 = Poor; 0.2 = Slight; 0.4 = Fair; 0.6 = Moderate; 0.8 = Substantial; 1.0 = Almost Perfect.

Summary of Measures and Statistical Concepts

Meta-analyses were conducted for the results of effect size estimates (Hedges'g), publication bias, moderators and sensitivity analyses using the Comprehensive Meta-Analysis (CMA) software version 2.0. According to Durlak (2009) and Hedges and Olkin (1985), Hedges'g is a good choice of effect size estimates with pooled variance using (n-1) for each sample that restrictively and accurately correct bias in trials using smaller sample sizes. It can be, in the simplest form before correction, calculated by the standardized mean difference of the experimental group (CBT; $\tilde{Y}_e$) and control group ($\tilde{Y}_c$) divided by pooled standard

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deviations (SD_{pooled}):

$$g = (\tilde{Y}_e - \tilde{Y}_c)/ SD_{pooled}$$

Given that the effect sizes differ because of sampling error and random variation from unknown distribution, random-effect model rather than the fixed-effect model is deemed more appropriate for meta-analysis (Borenstein et al., 2010). The magnitude of Hedges'g was interpreted using Cohen's (1988) effect sizes (0.2 = small; 0.5 = medium; > 0.8 = large)

Synthesis of the Results

The study compared the effect sizes (Hedges'g) of experimental group (CBT) and that of control group on PSD measured by Beck Depression Inventory (BDI; Beck et al., 1996) or Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). The within-study and between-study comparison at post-treatment were conducted using CMA version 2.0. BDI (Beck et al., 1996) and HAM-D (Hamilton, 1960), which are widely used to measure the severity of depressive symptoms, with moderately high to high Cronbach's Alpha (α) (.95 for BDI and .81 for HAM-D) and strong moderate convergent validity ($p < .01$) (Cahill et al., 2006).

Means, SDs, and sample size for CBT and control groups were needed to calculate Hedges'g in CMA 2.0. The researcher means and SD from studies or manually calculated the missing values from other reported data, such as median and interquartile range (presumed that the model followed Guassian distribution), Z-scores, T-scores, confidence-intervals (CIs) or standard errors.

Statistical heterogeneity of outcome measures was examined by Q-statistic, I-squared (I2), and tau-squared (τ2).

According to Huedo-Medina and colleagues(2006), Q-statistic would be able to identify the existence of heterogeneity beyond chance when $p < .05$; I2, which is an inconsistent index used to describe the extent of heterogeneity in percentage, considered heterogeneity beyond chance across studies when the value is over 50%; τ2 is used to quantify heterogeneity across studies and indicates heterogeneity when the value is over 0.05. These concepts of heterogeneity were applied to both main effect size comparison of CBT group and processed further in additional analyses.

Risk of Bias across Studies

Publication bias was examined using Egger's test of the intercept (β) with funnel plot and Egger's regression, as appropriate given the known limitations of these methods. In the test, the standardized effect, which is calculated by the effect size over standard error, was regressed on precision. Egger and colleagues (1997) found that in the studies with low publication bias, the intercept showed less deviation from zero, leading to a lower degree of asymmetry. The significance of p-value of the intercept was set at 0.1 levels.

Additional Analyses

Subgroup and Sensitivity Analyses

No subgroup analyses were conducted. Two sets of sensitivity analyses were conducted post-hoc to investigate potential sources of heterogeneity: 1) by excluding the study of Lincoln and Flannaghan (2003) as the outcome measure for PSD (using BDI) differed from other three studies (using HAM-D) with missing means and SDs (calculated from reported median and interquartile range); 2) by excluding the study of Alexopoulos et al. (2012) because of its distinctively small sample size (12 people for each group) was about one-third of those used in other three studies. All results of sensitivity analyses were

indicated by Hedges'g and inconsistency index (I2).

Meta-Regression Analyses

To investigate other potential sources of heterogeneity or moderators, six factors were selected for meta-regression: mean age; HAM-D score in baseline; percentage of participants undergoing antidepressants therapy during the CBT intervention; average methodological quality by two raters; intensity of CBT, as calculated by time per session in minutes multiplied by number of sessions; and post-treatment follow-up months. The method of unrestricted maximum likelihood in the linear regression model was employed to calculate the intercepts (β) and p-values for the association between each pair of moderators and effect size.

Results

Study Selection

Initially, online databases and the manual search yielded l,831 literature sources (see Figure 1). All titles were sorted in ascending order in Excel file, and about 60% (1,094) were excluded because of duplication. The remaining underwent screening of the title and abstract; 94.6% (697) were excluded because of obviously mismatched research designs (non-RCTs), treatment (by drug only), or outcome measures (functional mobility measures only). A full-text screening was conducted for the remaining peer-reviewed studies, of which 10% (4) met the prescribed inclusion criteria fully and were included in the qualitative synthesis and meta-analysis. No discrepancy between the assistant and researcher on the screening existed as the differential criteria for study selection were clear and straightforward.

Study Characteristics

The four included studies were all parallel- group and superiority trials of explanatory RCTs (Alexopoulos et al., 2012; Chang et al., 2011; Lincoln & Flannaghan, 2003; Mitchell et al., 2009). Details of the basic characteristics, research design, and findings are summarized in Table 1.

Two studies were from the United State, one from the United Kingdom, and one from China. In all studies, the researchers recruited community participants with PSD from public hospitals (three from rehab-hospitals and one from an acute-care hospital). However, exclusion criteria of the four studies were not concordant. Regarding the more commonly agreed criteria, three studies excluded participants with dementia, aphasia, and those with psychotic disorder, respectively; two excluded non-English speakers. The most inconsistent criterion was the type or duration of stroke; one study excluded those having a stroke within less than 1 month, one excluded young stroke, and one excluded first onset or hemorrhagic stroke. For identification of depressive symptoms on recruitment, only two studies specified formal diagnosis with DSM-IV criteria; the other two reported inclusion criteria for BDI or HAM-D scores only.

META-ANALYSIS OF CBT FOR PSD

TABLE 1. Overview of selected studies for community-dwelling subjects with post-stroke depression (characteristics and findings)

Trials	Country Place of recruitment	Exclusion criteria	Identification of depression	Demographic characteristics (Baseline)	Treatment		Sample Size		Drop Out		Primary measures of depression
					CBT	Control	CBT	Control	CBT	Control	
Lincoln & Flannaghan. 2003	UK (Nottingham Hospital)	-blind deaf -unable to speak English -had dementia (MMSE 23) -treated depression within 5 years -living outside -BI 10 1 month post-stroke	BDI 10 or WDI 18	Male – 51% Age – 66.1±13.3 Post-Stroke by month(s) – 1(49.5%), 3(21.9%), 6(28.6%)	CBT	No contact after screening	39	41	5	5	BDI
Chang et al., 2011	Shandong, China (Rehab center for disabled people)	-traumatic brain injury -history of mental illness -cognitive impairment (MMSE 23) -severe aphasia	HAM-D	Male – 43%; Age – 58.9±10.4 Post-stroke days – 136.29±69.1 (4.5±2 months) Stroke type: Ischemic (65.2%), Hemorrhagic (34.8%) Married – 71.2% Education: University (37.9%) Pre-stroke stress event – 63.6%	KBT (REBT) – Regular Therapy	Regular Therapy	34	32	5	6	HAM-D
Alexopoulos et al., 2012	USA (Burke rehab hospital)	-age 60 -moderate-severe dementia (MMSE 20) -moderate aphasia (NIHSS Best Language 1) -psychotic depression (DSM-IV) -suicidal -non-English speaker	Unipolar depression (DSM-IV) by clinician	Male – 58.3% Age – 70.9±8.5 Education – 15 years Stroke episode – 1.37±0.67	EFT	ESD	12	12	3	1	HAM-D
Mitchell et al., 2009	USA (4 acute care hospitals in Seattle or Wash)	-hemorrhagic stroke -1st onset of stroke -aphasia -GCS 15 -psychosis	DSM-IV GDS 11	Male – 61%; Age – 57±31.4 Stroke Type: Ischemic (100%) Married – 40% Race – over 60% white History of Depression – 70% Right-hemi: CBT (62.5%), Control (47.2%)	PSBI · Antidepressant	Usual Care · Antidepressant	47	53	3	5	HAM-D

TABLE 1. (Continued)

Trials	Outcome measures (Depression)	Method(s) of statistical analysis used	Intention-To-Treat (ITT)	Results			Limitation
				Sig.?	Any improvement?	Key findings	Difficulty reviewing
Lincoln and Flannaghan, 2003	BDI	Kruskal-Wallis One-way ANOVA	No	No	Yes (mild drop in all groups)	(Baseline) Significant difference was found in allocation of depression in CBT group (p .05) than other groups (Post-treatment) Unable to prove that CBT was more effective to minimize depression level in PSD (p .05)	-claimed no treatment for depression within 5 years, but at the end reported that 1 3 subjects were undergoing antidepressant therapy (36% for CBT; 32% for control) -competency of CPNs to conduct CBT with limited training -limited information of type of stroke and other health-related factors (any covariates?)
Chang et al., 2011	HAM-D	T-test 2x2(time x group) ANOVA	No	Yes	Yes	(Baseline) Women and having experience of pre-stroke stressful event showed significantly higher severity of depression (Post-treatment) Both control group (t -4.0, p .001) and CBT group (t -8.13, p .001) showed significant improvement from baseline, with time-group interaction effect (F 27.64, p .001). CBT with regular therapy in PSD was more effective than using regular therapy alone (t -5.35, p .001)	-unable to identify whether the reduction of depression was attributing to education itself or with behavioral component -assistive help offered to low-educated elderly with difficulty understanding body-mind concept might affect treatment consistency -anger management as a part distinctive from other CBT; this factor was highly associated with depression (p .01), may alleviate depression directly or indirectly (moderator?) - claimed the sample was from rural with higher rate of depression and disability (any threats to external validity?)
Alexopoulos et al., 2012	HAM-D	Mann-Whitney U · Chi-square Odd ratio for remission rate	Yes	No	Yes	There was a trend (p .054) that CBT was more effective than control in reducing depressive symptoms, but not significant. -Rate of remission†: 66.7% for CBT, 16.7% for control	(Baseline) High Performer in Stroop color test was allocated to CBT group, 31.3±8.2 vs. 14.6±10.8 for control -small number of subjects (12 for each group) -more bias when the therapy provider was the same person in both groups w o blinding
Mitchell et al., 2009	HAM-D	ANCOVA Logistic regression for remission (Yes No)	Yes	Yes	Yes	CBT was more effective than control in reducing depression and improving remission rate at treatment-ended (p .05, for both), but no lasting effect for symptom reduction at follow-up 12 months later (p .108). -Rate of remission†: 48% for CBT, 27% for control	-subjects on antidepressant therapy: 62.4% (baseline) to 77% (during treatment) - no standardized dose and type of drug - the author claimed that the treatment of depression in this study was less effective than that with short-term outcome and motivational interviewing technique (critical factor?)

Note. NS Not specified;

† "Remission" is operationally defined as score of HAM-D 9

Abbreviations:

BDI Beck Depression Inventory; BI Barthel Index; CBT Cognitive Behavioral Therapy; CPNs Community Psychiatric Nurses; DSM Diagnostic and Statistical Manual of Mental Disorders; EFT Ecosystem-Focused Therapy; ESD: Education on Stroke and Depression; GCS Glasgow Coma Scale; HAM-D Hamilton Rating Scale for Depression; KBT Knowledge and Behavioral Therapy; MMSE Mini-Mental State Exam; NIHSS National Institutes of Health Stroke Scale; PSBI Psychosocial-Behavioral Intervention; PSD Post-Stroke Depression; Psy. Psychology REBT Rational-Emotive Behavioral Therapy; WDI Wakefield Depression Inventory

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Participants

All studies reported gender proportion and mean age on successful recruitment ranged from 43 to 61% (male) and from 25 to 88 years old, respectively (see Table 1).

Two studies reported average post-stroke time of 2.87 months and 4.5 months. Two studies reported percentages of ischemic stroke at 65.2% and 100%, respectively. Other demographics were selectively reported by different studies. For example, one study reported over 70% of participants were married, and about two-thirds had experienced pre-stroke stressful events.

Another study reported 40% were married. A third study reported 70% of participants with histories of depression.

In total, 270 participants were recruited in the four studies; using random selection, the CBT/control ratio was 49:51. Twelve participants (four for CBT and eight for controls) who dropped out of the treatment were not included in the meta-analysis. The final ratio of CBT/control for the analysis was approximately half-half. The drop-out rates in the CBT and control groups were 3.0% and 5.8%, respectively.

TABLE 2. Details of the quality of CBT

Trials	Name/ components of CBT group (face-to-face, for all)	Time per session (hours)	Frequency (week)	Total sessions	Follow-up duration (month)	Background of CBT providers	Co-therapy offered	Standardized training/ Supervision	Quality of CBT evaluation
Lincoln and Flannaghan, 2003	CBT -education -graded task assignment -activity scheduling -identifying & modifying irrational thoughts beliefs	1	1	10	3	CBT Research CPNs Assessment Assistant psychologist	No	trained and supervised by cognitive therapists	NS
Chang et al., 2011	KBT (REBT) (knowledge) -health psy. & recovery for lifestyle risks changes (behavioral) -belief changes -forgiveness -anger management	1-2	1	4	1	Psy. graduate	Regular Therapy -Antidepressants -Rehab training for physical functioning	NS	NS
Alexopoulos et al., 2012	EFT -education direct suggestions -CBT problem-solving skills -goal setting & planning for clients and their family	0.75	1	12	No	(74 therapists) NS	No	trained 6 cases studies with manual and supervised by medical staff	-audiotaped -rated by reviewers using EFT Fidelity Scale (EFTFS)
Mitchell et al., 2009	PSBI -CBT - problem solving technique coping strategies for physical and cognitive difficulties	0.5-1 (depends on client's fatigue)	1	9	12	Certified nurse (APN specialized in mental health) with master's degrees♦	Antidepressants (SSRI)	supervised by clinical psychologists for case discussion on monthly basis♦	-audiotaped♦ -listened to about 10% of recorded sessions for fidelity evaluation♦

Note. NS Not specified.

Abbreviations:

APN Advanced Practice Nurse; CBT Cognitive Behavioral Therapy; CPN Community Psychiatric Nurse; EFT Ecosystem-Focused Therapy; KBT Knowledge and Behavioral Therapy; REBT Rational-Emotive Behavioral Therapy; PSBI Psychosocial-Behavioral Intervention; Psy. Psychology

♦ Additional data were provided by author on request by e-mail

Treatment Quality of CBT

Table 2 shows the detailed components, administration, and quality parameters of CBT. Four studies considered using CBT as the primary intervention in different names (CBT, KBT, EFT, and PSBI). All reported details of number and time of CBT sessions enabled the researcher to calculate treatment intensity by "time per session multiplied by the number of sessions" ranged from 360 to 600 minutes. Three studies reported one-off post-treatment follow-up ranged from 1 month to 12 months; the remaining studies reported no follow-up after treatment.

The background of CBT providers was taken into consideration. Two studies were conducted by registered nurses, one by a graduate student in psychology, and one by therapists without a specific description of their professional qualifications. All studies allowed co-therapy, particularly two that overtly applied antidepressant therapy for both the CBT and control groups as usual care. Three studies specified standardized training or supervision for CBT providers; only two reported the use of standardized fidelity scales and audio typing devices for quality monitoring.

Risks of Bias within Studies

The overall Cohen's Kappa for methodological quality of four RCTs was 0.83 (range from 0.6 to 1 for each study; $p < .01$), which indicates that the inter-rater consistency reached substantial levels (see Table 3). Over 93% of items had the same score as rated by V and KC. In sum, two studies were rated as low (2.5-3), one as moderately high (6.5), and one as high (8) for methodological quality.

Outcome Measures and Results of Individual Studies

Three studies assessed depressive symptoms using HAM-D; only one study used the BDI. Table 1 (Continued) lists the description of research findings for each study. All studies provided clear sample sizes in the CBT and control groups; however, only two clearly stated the means and SDs of post-treatment outcomes. For the remaining, this researcher calculated the missing values manually by "median and interquartile range" and "change of scores from baseline and means and SDs in the baseline." Score reduction from baseline and post-treatment between-group difference in the CBT group for each study ranged from 2.64 to 10.97 and -2 to -6.65, respectively. Two studies showed significant between-group differences ($p < .05$ and $p < .001$), one showed a tendency of improvement in CBT ($p = .51$), and one showed no significant results ($p > .05$).

Synthesis of Results

Forest plots were generated to present the treatment effect of CBT compared with controls (see Figure 2). To exclude the possibility of randomization bias, pre-treatment effect estimates were conducted prior to post-treatment analysis. At baseline, the effect sizes (Hedges'g) for all individual studies (ranged from -0.07 to 0.23, $p > .05$) and in total (0.05, $p > .05$) were small, which indicates that the level of depression of CBT and controls were comparable after the randomization process. In the post-treatment phase, the CBT groups showed significant reductions in depressive symptoms compared with controls (Hedges'g [95% CI] = -0.52 [-0.78, -0.25], $p < .001$). Only a small degree of heterogeneity existed in the outcome measures of depression ($I2 = 0.12$; $\tau 2 = .01$; $Q(3) = 3.42$, $p > .05$).

TABLE 3. Methodological quality of included RCT studies

Trials/ Items	Lincoln and Flannaghan. 2003	Chang et al.. 2011	Alexopoulos et al., 2012	Mitchell et al., 2009
Generalization of Allocation Sequence	Adequate (2)	NS (0)	NS (0)	Adequate (2)
Allocation Concealment	Adequate (2)	NS (0)	NS (0)	Adequate (2)
Standardization of Treatment	Partial (1)	Adequate (2)	Adequate (2)	Adequate (2)
Blinding	Assessor (2)	NS (0)	NS (0)	Assessor (2)
Adequate Follow-up	Adequate (2)	Partial (1)	No (0)	Adequate (2)
Sample-size Calculation	Yes (2)	NS (0)	NS (0)	Yes (2)
Description of Withdrawal	Yes (2)	Yes (2)	Yes (2)	Yes (2)
Intention-to-treat	NS (0)	NS (0)	Yes (2)	Yes (2)
Sum of Rating				
Rater 1 (V)	7	3	3	8
Rater 2 (KC)	6	2	3	8
Methodological Quality †	Moderate to High	Low	Low	High
Cohen's Kappa(κ) of Raters	0.6	0.714*	1**	1***

Note. NS − Not specified;

( ) − Number of agreement of adequate quality by 2 reviewers:

0 = Both disagreed; 1 = Either Rater V or KC agreed (Partial); 2 = Both agreed (Adequate)

† Methodological Quality: 0-3 − Low; 4-6 − Moderate; 7-8 − High

* indicates significant difference at .05 level

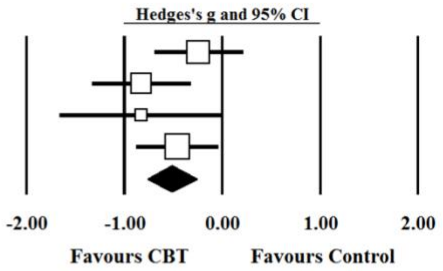
** indicates significant difference at .005 level

*** indicates significant difference at .001 level

Post-Treatment Effect of CBT in Post-Stroke Depression

Trials	CBT			Control					(Random Model)
	M	SD	Total	M	SD	Total	*p*-value	Weight	Hedges' g, [95% CI]
Lincoln and Flannaghan, 2003	15.00	7.42	38	17.00	8.90	38	.289	30.07%	-0.24 [-0.69, 0.21]
Chang et al., 2011	21.26	9.69	34	27.91	5.79	32	.001	25.02%	-0.82 [-1.31, -0.32]
Alexopoulos et al., 2012	8.20	6.63	12	13.20	5.37	12	.051	10.34%	-0.80 [-1.61, 0.01]
Mitchell et al., 2009	10.80	5.70	44	13.60	6.40	48	.029	34.57%	-0.46 [-0.87, -0.05]
Total (95%, CI)			128			130	.000	100%	-0.52 [-0.78, -0.25]

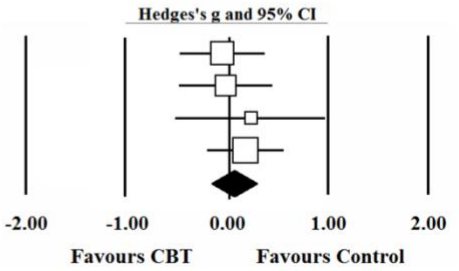
Heterogeneity: $Tau^2 = 0.01$; $Q(3) = 3.42$ ($p = .33$); $I^2 = 12.23\%$
Test for overall effect: $Z = -3.817$ ($p = .00$)



Baseline Between-Group Comparison in Post-Stroke Depression

Trials	CBT			Control					(Random Model)
	M	SD	Total	M	SD	Total	p-value	Weight	Hedges' g, [95% CI]
Lincoln and Flannaghan, 2003	17.50	6.68	39	18.00	7.42	41	.752	29.71%	-0.07 [-0.50, 0.36]
Chang et al., 2011	29.29	13.45	34	29.67	5.84	32	.883	24.51%	-0.04 [-0.51, 0.44]
Alexopoulos et al., 2012	22.30	6.89	12	20.40	9.19	12	.568	8.86%	0.23 [-0.55, 1.00]
Mitchell et al., 2009	20.53	4.53	47	19.8	4.15	53	.401	36.92%	0.17 [-0.22, 0.56]
Total (95%, CI)			132			138	.453	100%	0.05 [-0.18, 0.29]

Heterogeneity: $Tau^2 = 0.00$; $Q(3) = 0.96$ ($p = .81$); $I^2 = 0.00\%$
Test for overall effect: $Z = 0.44$ ($p = .66$)



Denotes: CBT = Cognitive Behavioral Therapy; M = Mean; SD = Standard Deviation; CI = Confidence Interval

FIGURE 2. Forest plots: Comparisons of the effect estimates (*Hedges'g*) of CBT and controls on reduction of Post-stroke depression in Post-treatment (Upper) and baseline (Bottom)

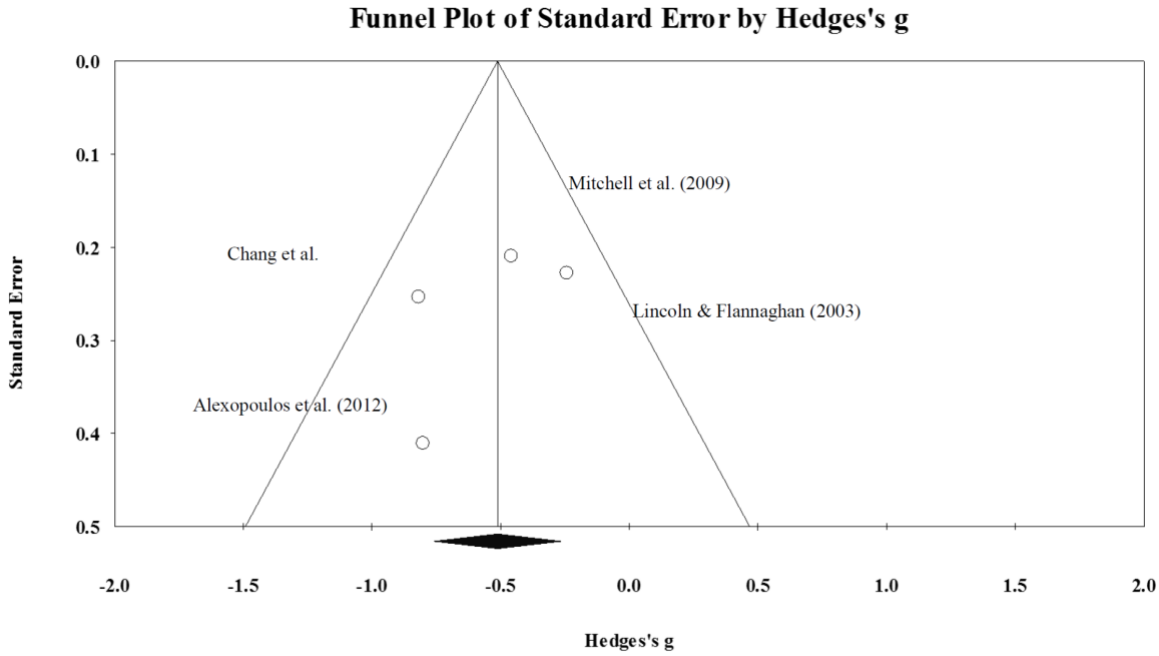


FIGURE 3. Funnel plot of standard error by *Hedges'g* for selected trials

Risk of Bias across Studies

Referring to Egger's test results, the intercept (β) of Hedges'g on the outcome measures for depression was -2.31 (95% CI = -12.82, 8.20), with t(2) = 0.94 (p = .44, two- tailed), which indicated no evidence of publication bias. However, a gap of missing values was found in the bottom right corner in funnel plot (see Figure 3). It implies that the studies with smaller sample sizes and non-significant results using CBT were less likely to be published in peer-reviewed journals.

Additional Analyses

Sensitivity Analyses

The main effect estimates including the four studies were used as the standard values for reference (Hedges'g [95% CI] = -0.52 [-0.78, -0.25], p <.001;
Heterogeneity: I2 = 0.12, p > .05). After excluding Lincoln and Flannaghan (2003) for the use of different outcome measures (BDI) and the missing values calculated by the researcher, the treatment effect on depression was not only significant but also larger (Hedges'g [95% CI] = -0.63
[-0.92, -0.34], p < .001) with almost no extent of heterogeneity
(I2 = 0.00, p > .05). In contrast, excluding Alexopoulos et al. (2012) for its small sample size decreased treatment effects (Hedges'g [95%CI] = -0.49 [-0.80, -0.18],
p < .001) and increased heterogeneity (I2 = 0.30, p > .05).

Meta-Regression Analyses for

Moderators

In meta-regression analyses, data were retrieved from respective studies, except one missing value for the percentage of antidepressants. Referring to the linear regression model, age (β = -1.10, p = .49), HAM-D score in baseline (β = 0.53, p = .40), and percentage of participants undergoing antidepressant therapy during intervention (β = -0.18, p =.49) showed no significant association with the treatment effects of CBT. In contrast, methodological quality (β = -0.97, p < .001), intensity of CBT (β = -1.64, p < .01), and duration of post-treatment follow-up (β = -0.60, p < .001) showed significant and negative associations with the effect (see Figure 4).

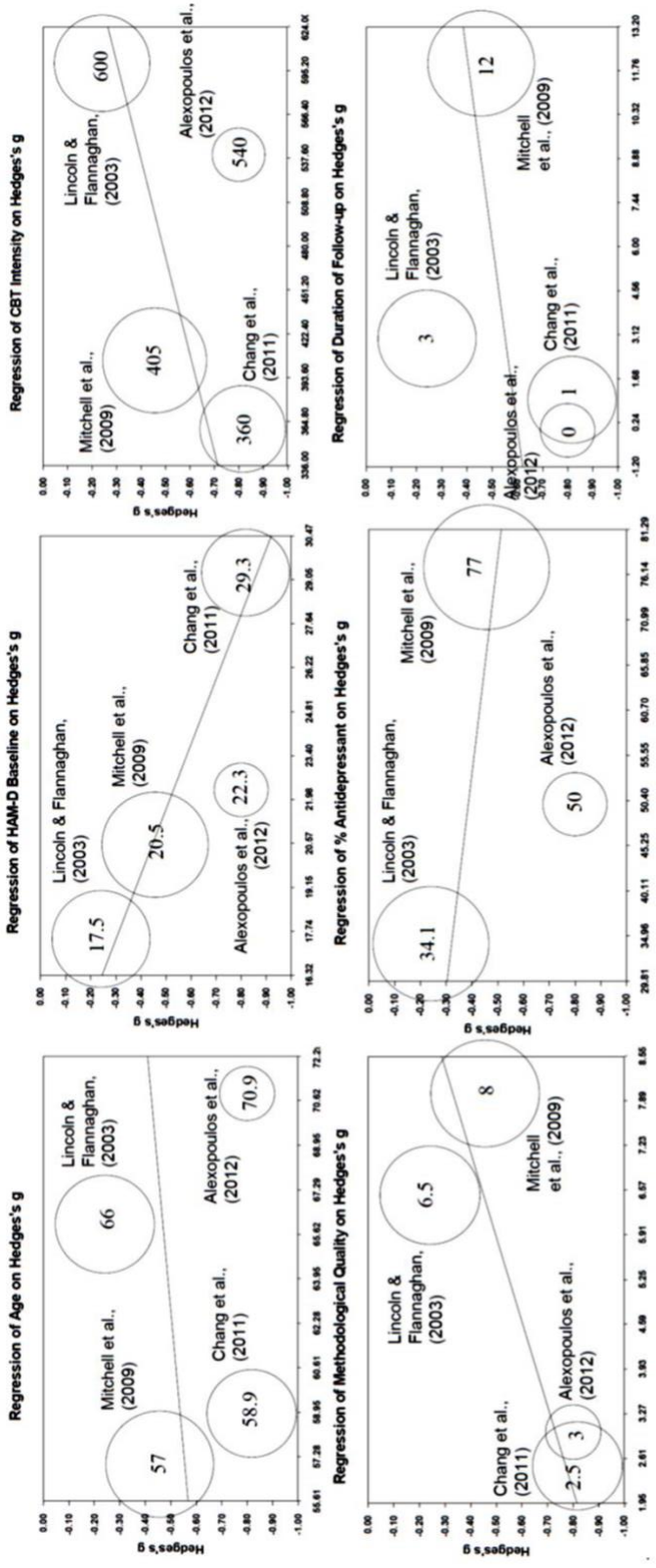
Discussion

Summary of Evidence

After a literature search and screening, four RCTs about the treatment effects of CBT in individuals with PSD were included and synthesized for further analyses. The total model of effect sizes showed significant medium post-treatment effects (Hedges'g = -0.52, p < .001), which indicate the relative superiority of CBT in reducing depressive symptoms. Little heterogeneity (accounting for 12%) was detected at non-significant levels. The results of the additional analyses and potential bias are discussed.

Quality of Recruitment

The type of stroke and depression on baseline varied from study-to-study; for example, young vs. old, first vs. recurrent stroke, ischemic vs. hemorrhagic, acute vs. sub-acute phase, left- vs. right-hemi, and severe vs. moderate depression. It is believed that the non-concordant exclusion criteria of individual studies with large variation may lead to biased results. For instance, people with recurrent stroke were less likely to benefit from CBT because of poorer health conditions than their first-stroke counterparts (Yuan et al., 2012).



Trials	Age (year)	HAM-D (baseline)	% of receiving Antidepressant	Method Quality	CBT Intensity (mins)	Duration of FU (months)
Lincoln and Flannaghan, 2003	66.0	17.5	34.1	6.5	600	3
Chang et al., 2011	58.9	29.3	NS	2.5	360	1
Alexopoulos et al., 2012	70.9	22.3	50.0	3.0	540	0
Mitchell et al., 2009	57.0	20.5	77.0	8.0	405	12
Intercept (β_0)	-1.10	0.53	-0.18	-0.97	-1.24	-0.60
P-value	0.49	0.40	0.49	0.00	0.00	0.00

HAM-D = Hamilton Rating Scale for Depression
FU = follow-up

FIGURE 4. Regression graphs of moderators on Hedges' g using method of Unrestricted Maximum Likelihood

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With limited information of demographics, the most possible threats of selection or confounding bias, except age and severity of depression, were not covered in this review.

Quality of RCT

Methodological quality may strongly affect the quality of review based on the "garbage- in-garbage-out principle" (Borenstein et al., 2009). Despite the substantial objectivity of raters (κ = .83, $p < .01$), the results of quality ratings were irregularly distributed to both ends (low = 2; moderately high = 1; high = 1). Interestingly, only two items (7% of all) were rated differently. Raters discussed the reasons for rating and found that the terms, "standardization of treatment" and "adequate follow-up" were ill-defined. They felt struggled to identify standardized- and individualized- care when session plans were not clearly described. For example, in Chang et al. (2011), rater V used length- dependent reference and judged that post- treatment follow-up at 1 month was considered adequate for short-term CBT (four sessions completed in 1 month); however, KC rated "inadequate" with a judgment on fixed reference (3 months as a cut-off) regardless of intensity of CBT.

Quality of CBT

The researcher thought that the most critical part of this review was to identify appropriate studies of CBT and to assess treatment quality. Perhaps all CBT shared common components and the variation of sessions in different trials would strongly affect the treatment outcomes. Moderator analyses proved that studies with higher scores in methodological quality, more intense CBT, or longer duration of post- treatment follow-up showed better improvement in depression with CBT.

Limitations

First, a paucity of research studies yielded a threat of external validity, which limits generalization to other population of stroke sufferers. Despite the low drop-out rate, small sample sizes potentially exaggerated the true effects of CBT as reflected by sensitivity analysis (Alexopoulos et al., 2012). Additionally, the few studies included making identification of reporting preference complicated. Although no publication bias was identified using Egger's test ($p > .05$, two-tailed), the methods of its detection might be underpowered with a small number of trials selected for analysis.

Second, the researcher evaluated the effect size estimates of all studies regardless of outcome measures in consideration of the significant convergent validity of BDI and HAM-D and small sample size. A sensitivity analysis (Lincoln & Flannaghan, 2003) found that the effect of CBT would be suppressed with the magnitude toward controls. Paradoxically, it made the statistical findings more restrictive instead.

Third, the effect of co-therapy was unknown. Although the researcher found that antidepressant therapy was not likely to impede the effectiveness of CBT, adjunctive techniques, such as a general rehab-program, relaxation exercise, and anger management were not examined. One study (Chang et al., 2011) with the highest effect size in the review distinctively applied anger management skills in the CBT sessions. The study reported a high association between treatment outcomes and anger elements, which could raise doubts about whether anger management training contributed to the alleviation of depressive symptoms.

Implication and Future Research

This is the first study which reviewed four RCTs systematically on the effectiveness of CBT for PSD sufferers in the community using a comprehensive research design and meta-analytic method. In summary, CBT is effective in dealing with PSD. The

researcher speculated three possible explanations for the scarcity of literature: 1) inadequate knowledge of the effectiveness of CBT in PSD; 2) costly, time-consuming, and labor-intensive to conduct RCTs in CBT; and 3) lack of hope or motivation for stroke sufferers with PSD. This review can help tackle challenges by promoting the positive aspect of CBT in dealing with PSD to the public, supporting practitioner grant funding with synthesized evidence, and motivating clients to accept CBT for positive changes of mental wellness.

To minimize the variation in treatment design, a standardized protocol with an operation manual of CBT particularly for PSD seems necessary to enhance professional training for CBT providers and treatment quality for future studies. The researcher expected that more quality RCTs (Kootker et al., 2012; Visser et al., 2013) of CBT in PSD would be conducted to improve the overall health condition of stroke sufferers and minimize the burden on their relatives, health-care professionals, and even tax-payers within the community. Further subgroup analyses (e.g., individual vs. group CBT) on PSD will be implemented when the availability of literature and completeness of data are satisfactory.

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Compliance with Ethical Standards

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Conflict of Interest: The author declares that he has no conflict of interest.
Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.
Informed Consent: It is not applicable to meta-analysis.

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