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Beneficial effects of non-pharmacological interventions for post-stroke pain: A meta-analysis

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Abstract

Purpose: Pain is a frequent post-stroke health concern, and several non-pharmacological interventions are commonly employed to manage it. However, few reviews have examined the effectiveness of such interventions, making it difficult to draw conclusions about their usefulness. Furthermore, subgroup analysis based on post-stroke pain level or intervention characteristics is rarely performed. This study aimed to investigate the effectiveness of non-pharmacological interventions and evaluate the significant factors associated with post-stroke pain through subgroup analysis.

Design: Systematic review and meta-analysis.

Methods: Relevant studies were obtained from seven databases, from their commencement up to March 2024, as well as from the gray literature. The PICOS approach was used to evaluate the eligibility criteria of the studies. The RoB-2 tool was used to determine the risk of bias in each randomized trial. Pooled estimations of standardized mean difference and heterogeneity (quantified with I^2) were obtained using a random-effects model. The stability of the pooled result was then assessed using the leave-one-out approach. STATA 17.0 was used to run the meta-analysis.

Findings: Non-pharmacological interventions were effective in reducing pain immediately after intervention (pooled SMDs: −0.79; 95% confidence interval [CI]: −1.06 to −0.53; $p < 0.001$). The approach involving acupuncture, aquatic therapy, or laser therapy and rehabilitation training was effective for post-stroke hemiplegic shoulder pain. A pooled analysis of non-pharmacological interventions showed that both less than 4 weeks and more than 4 weeks of interventions were effective in alleviating pain in stroke patients.

Conclusion: Non-pharmacological approaches appear to be beneficial for reducing post-stroke pain. The outcomes based on the modalities merit further research.

Clinical relevance: Further studies are needed to determine the effects of different modalities on pain intensity following a stroke. Furthermore, to avoid overestimation of intervention efficacy, future randomized trials should consider blinding approaches to the interventions delivered.

KEYWORDS
meta-analysis, non-pharmacological, pain intensity, pain management, post-stoke pain

Pain is a common post-stroke health problem, but its complications are still poorly understood. Around 11%–42.73% of patients experience post-stroke pain in both the acute and the chronic phase (Liampas et al., 2020; Paolucci et al., 2016). The term "post-stroke pain" refers to a syndrome that is frequently associated with post-stroke health problems, with the most common subtypes of post-stroke pain being central post-stroke pain, complex regional pain syndrome, shoulder pain, spasticity-related pain, and headache (Delpont et al., 2018; Hansen et al., 2012). Various types of post-stroke pain appear at one to six months (de Oliveira et al., 2012; Hansen et al., 2012; Raffaeli et al., 2013), even up to 5 years (Westerlind et al., 2020), after the stroke.

The impact of post-stroke pain can be felt both in the early phase and in the long term. In the early phase, within 3 months after a stroke, post-stroke pain is linked to the onset of anxiety symptoms in patients (Bovim et al., 2018; Hartley et al., 2022). Over the longer term, more than three to six months after a stroke, post-stroke pain has a moderate to severe effect on daily activities (Hansen et al., 2012; Lindgren et al., 2018) and leads to a lower quality of life (Hartley et al., 2022; Payton & Soundy, 2020; Tang et al., 2015). In addition, assessment of post-stroke pain can be challenging; for example, patients may fail to communicate their pain due to aphasia, loss of motor skills, neglect, or cognitive impairment (Delpont et al., 2018; Soares et al., 2018). Careful investigation, based on the patient's condition during pain assessment, is highly important (Edwards et al., 2020; Harrison & Field, 2015; Yang & Chang, 2021) to prevent inappropriate evaluation which can result in suboptimal pain management (Nesbitt et al., 2015; Paolucci et al., 2016).

Various approaches, including pharmacological and non-pharmacological, are used for pain management. Although the main treatment for post-stroke pain is pharmacological (Bae et al., 2014; Ri, 2022), non-pharmacological approaches have increased in use in recent years (Liu et al., 2019; Ma et al., 2022; Malfitano et al., 2021). Non-pharmacological approaches, such as acupuncture therapy, appear to be effective for improving motor function, pain relief, and activities of daily living in post-stroke patients with shoulder–hand syndrome (Liu et al., 2019). Repetitive transcranial magnetic stimulation is associated with decreased chronic pain and changes in motor cortex excitability in cases of subacute central post-stroke pain (Malfitano et al., 2021). A case report showed the success of mirror therapy for pain reduction in chronic thalamic stroke patients (Corbetta et al., 2018).

Although post-stroke pain has been extensively studied, only one review quantitatively examined the impact of non-pharmacological approaches on post-stroke pain (Xu et al., 2020); however, the conclusions of the study were limited and the researchers were unable to perform subgroup analysis on the important characteristics of post-stroke pain due to the very few trials ($n=4$) included in the meta-analysis. Furthermore, the researchers did not consider other types of post-stroke pain. Therefore, the benefits of non-pharmacological approaches specific to aspects of post-stroke pain need further discussion. Another review of 18 studies published in 2016 provided qualitative findings only, making it difficult to objectively evaluate the true effect of non-pharmacological interventions for post-stroke pain (Akyuz & Kuru, 2016). Although several studies have reviewed the effectiveness of non-pharmacological interventions for post-stroke pain management, none have evaluated the effects of interventions based on pain characteristics and dose response which may lead to different outcomes. The purpose of this study was to investigate the effectiveness of non-pharmacological interventions, as well as to evaluate the significant aspects associated with post-stroke pain using subgroup analysis.

MATERIALS ANDS METHODS

The Cochrane-recommended Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed in this systematic review and meta-analysis (Page et al., 2021), see Data S3. The study protocol was registered on the PROSPERO International Prospective Registry of Systematic Reviews on August 20, 2023, with registration number CRD42023405191.

Search methods

A structured search of seven databases—CINAHL, Cochrane Library, EMBASE, Medline, OVID (UpToDate), PubMed, and Web of Science—from database inception to March 2024 was performed. In addition to the seven databases, the gray literature was also searched using Google Scholar to find relevant trials. The medical subject headings (MEsH) included stroke, non-pharmacological, and randomized controlled trial. A summary of search methods is provided in Data S1.

Eligibility criteria

The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework was used to determine the eligibility criteria for each trial included in this study (Amir-Behghadami & Janati, 2020). The following five elements were used as the inclusion criteria in this study when searching the literature: population (**P**)—stroke survivors regardless of age, gender, race, or stroke characteristics, such as type of stroke, onset of stroke, first stroke; intervention (**I**)—non-pharmacological therapies were employed in either hospital or independent health care settings; comparison (**C**)—usual care based on any form of therapy such as usual care or conventional therapy; outcome (**O**)—overall score for post-stroke pain conditions such as central post-stroke pain, complex regional pain syndrome, spasticity pain, and hemiplegic shoulder pain; and study design (**S**)—a randomized controlled trial was used to investigate the effectiveness of non-pharmacological therapies for post-stroke pain. Studies that were protocols, did not provide the mean and standard deviation (SD) for all conditions, and were of poor methodological quality, as assessed by a revised Cochrane risk-of-bias instrument for randomized trials (RoB-2), were excluded.

Study selection and data extraction

The study selection process was conducted by two researchers (IDS and IS). In the first round, they independently screened the titles and abstracts against the inclusion criteria. Following the first round, they independently assessed the full-text articles of relevant studies against the eligibility criteria. A first researcher (IDS) retrieved data from the included literature and a second researcher (IS) double-checked the data extracted, including the citation of the trial, the location of the trial, the number of samples in the trial, age, stroke characteristics such as type and onset, pain characteristics such as pain location, type of post-stroke pain, intensity of pain, and pain duration, intervention characteristics such as type of intervention, duration and follow-up of the intervention, measurement of pain, and mean and SD of pain before and after intervention in all conditions. In the case of disagreements arising during the process, a consensus was reached after discussing the differing points of view.

Risk of bias

RoB-2 with five domains was used to evaluate the methodological quality of each study. The five domains were risk of bias owing to the randomization method, risk of bias owing to deviations from the planned, risk of bias owing to missing outcome data, bias in outcome measurement, and bias in the selection of the reported outcome. For each domain, the risk of bias was classified as "high," "unclear," or "low." Studies that were recognized as having a high risk of bias in more than two domains were excluded from the current review. Two researchers (IDS and IS) independently evaluated the methodological quality of all included studies. Consensus on the diverse points of view evolving during the process was reached through discussion. Second, Egger regression was used to examine the influence of publication bias on the pooled standardized mean differences (SMDs) (Egger et al., 1997; Lin & Chu, 2018). The threshold for statistical significance was set at $p < 0.05$.

Statistical analysis

To begin the statistical synthesis, continuous data (mean and SD of all conditions) were converted into standardized mean difference (SMD) (Lipsey & Wilson, 2001). Given the variety of instruments used to assess post-stroke pain (Numeric Rating Scale, Numeric Pain Rating Scale, and Visual Analog Scale), SMD (Cohen's *d*) was computed to determine the magnitude of the effect of each trial (Lin & Aloe, 2021; Lipsey & Wilson, 2001). A random-effects model was used to pool the SMDs and analyze the heterogeneity of the pooled effect. The heterogeneity of the random-effects model was assessed using *Q* and I^2 scores, with a cutoff of >75% for significant heterogeneity (Higgins et al., 2003). The SMDs were pooled using a forest plot, and the bias of the meta-analysis was visualized with a funnel plot. The threshold for statistical significance was set at $p < 0.05$. Stata software, version 17 (Stata-Corp, College Station, TX, USA), was used to conduct the meta-analyses.

Sensitivity analysis

Sensitivity analysis was conducted using a leave-one-out strategy to assess the stability of the overall pooled SMD when one trial was omitted from the forest plot (Vehtari et al., 2017; Willis & Riley, 2017). The threshold for statistical significance was set at $p < 0.05$.

RESULTS

Study selection

The systematic search of seven databases generated 864 results. After performing an automatic tool duplication of EndNote 20 prior to screening, 332 records were deleted, leaving 532 records. The remaining records were evaluated for their title and abstract in accordance with the study's eligibility criteria. A total of 532 records were excluded, leaving 27 records for full-text evaluation, of which 18 were eliminated. After a thorough search, nine trials remained. Additionally, gray literature and previous reviews contributed five more papers. Eventually, 14 studies were included in the analysis (Bae et al., 2014; Choi & Chang, 2017; de Oliveira et al., 2014; Fan et al., 2012; Gwak et al., 2009; Ko et al., 2007; Korkmaz et al., 2022; Liu et al., 2015; Ojala et al., 2022; Park et al., 2011; Pérez-de la Cruz, 2020; Saha et al., 2021; Zhao et al., 2021; Zheng et al., 2018); see Figure 1.

Study characteristics

Five trials were conducted in South Korea, four in Spain, two in China, and one each in Brazil, Finland, India, and Turkey. The 14 studies involved a total of 599 post-stroke patients ranging in age from 30.0 to 65.7 years. The majority of stroke patients had either an ischemic or a hemorrhagic stroke, with survivors suffering from stroke ranging from 2 weeks to 5.2 years. Despite not all studies offering a thorough description of pain, the investigation uncovered that pain was felt in the upper and lower limbs, face, torso, shoulder, and knee. Furthermore, the pain level varied from moderate to severe and lasted from 2 days to 64.2 months.

The intervention group received a variety of interventions, including non-invasive brain stimulation; transcranial direct current stimulation and repetitive transcranial magnetic stimulation; bee venom acupuncture, four knee acupoints, and other types of acupuncture; mirror therapy and rehabilitation training; laser therapy; aquatic Ai Chi therapy; hydrotherapy; and dry land therapy. Individuals allocated to the control group received a sham

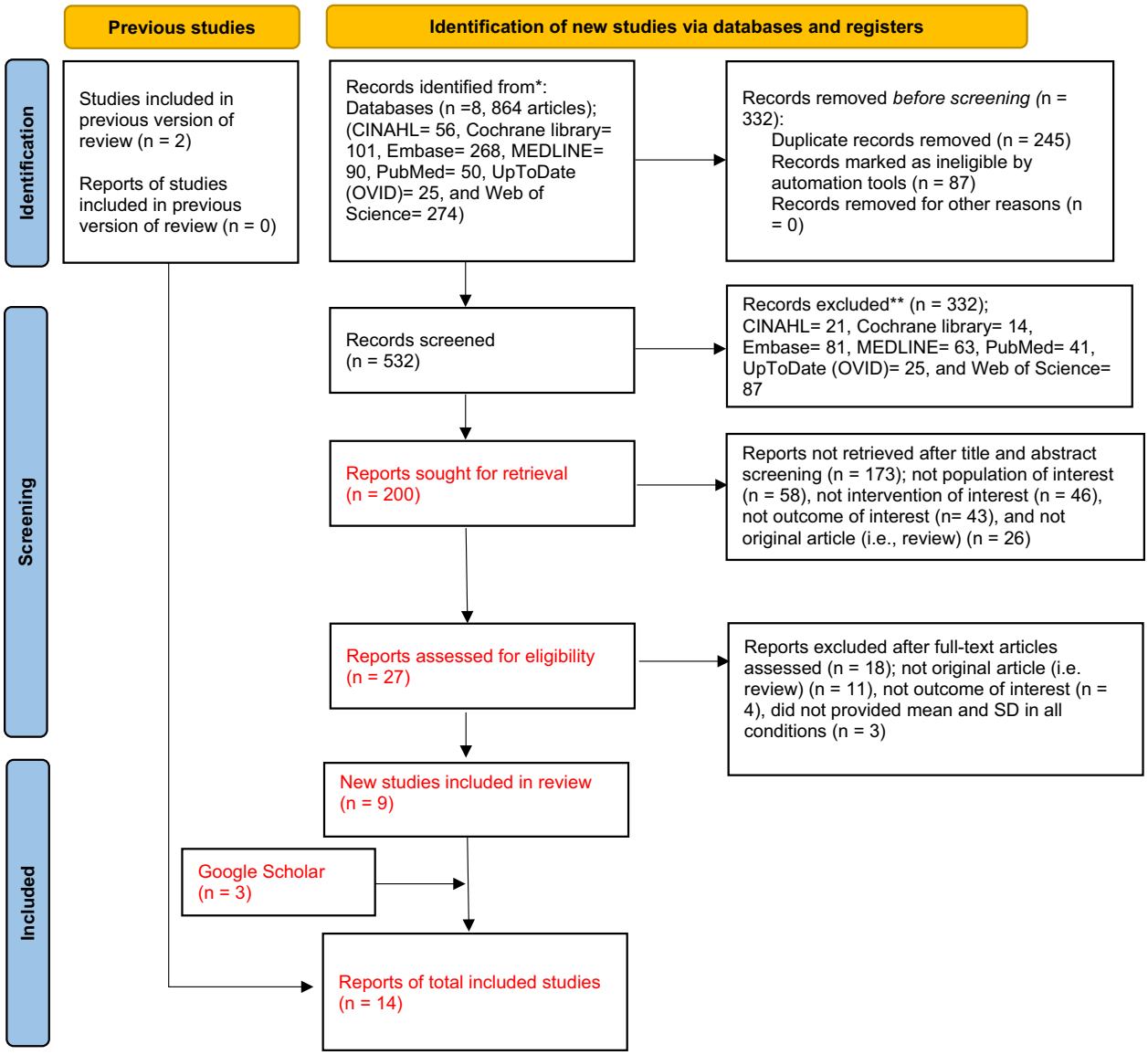


FIGURE 1 PRISMA flowchart diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

simulation, placebo, dry land therapy, Western medicine, herbs, or usual rehabilitation care. The duration of the intervention ranged from 10 days to 12 weeks, with follow-up ranging from immediately after the intervention to 4 weeks. Study characteristics are summarized in Table 1.

Publication bias

The RoB-2 tool was used to evaluate the methodological quality of the identified trials. Nonetheless, the analysis also highlighted the possibility of bias arising from deviations from the intended interventions due to participants and intervention providers not being blinded to group assignment (see Data S2). Due to the potential for methodological bias contributing to substantial heterogeneity, one study (Pérez-de la Cruz, 2020) out of the 14 included studies was excluded from the pooled results of the overall effect immediately post-intervention on pain. The Egger regression test indicated that the impact of bias on the analysis was low for each outcome: overall pain ($t = 0.78$, $p = 0.449$); type of post-stroke pain ($t = 0.53$, $p = 0.610$); pain intensity ($t = -0.22$, $p = 0.826$); type of intervention ($t = 0.23$, $p = 0.827$); duration of delivery of intervention ($t = -0.50$, $p = 0.626$); and length of follow-up ($t = -0.83$, $p = 0.453$). Furthermore, the funnel plot visualization indicated that publication bias was small, with no notable outliers outside of the triangle; see Figure 2.

TABLE 1 Summary of included studies.

		Participant characteristics				Pain characteristics			
No.	Citation/country	Sample size	Mean age, 95% CI	Stroke cause	Post-stroke onset, 95% CI (month)	Pain location	Pain type	Pain duration, 95% CI (month)	Pain intensity 95% CI (scale)
1	Bae et al., 2014/South Korea	14	52.3 (2.8)/51.1 (3.1)	Ischemic and hemorrhage	14.50/14.70	Face, upper and lower extremity	CPSP	NR	4.3/4.3 (moderate)
2	Choi & Chang, 2017/South Korea	24	57.8 (8.9)/60.3 (7.1)	Ischemic and hemorrhage	11.80/12.6	Shoulder	HSP	NR	5.8/6.3 (moderate)
3	de la Cruz, 2020/Spain	45	62.7 (13.4)/63.8 (13.6)	NR	5.2 years/5.1 years	NR	NR	NR	5.4/6.2 (moderate)
4	de Oliveira et al., 2014/Brazil	21	57.8 (11.9)/55.0 (9.68)	NR	NA	Upper and lower limb, face, and hemibody	CPSP	50.1/64.2	6.8/6.8 (moderate)
5	Fan et al., 2012/China	22	NR	NR	NR	NR	Thalamic pain	NR	7.9/8.09 (severe)
6	Gwak et al., 2009/South Korea	20	58.9 (11.4)/59.9 (13.5)	Ischemic and hemorrhage	6.0/8.0	Upper extremity and hemibody with and without face	CPSP	NR	6.5/6.4 (moderate)
7	Ko et al., 2007/South Korea	46	67.5 (9.6)/64.3 (9.9)	Ischemic and hemorrhage	±6 months	Shoulder	HSP	±6 months	7.0/7.1 (moderate)
8	Korkmaz et al., 2022/Turkey	44	60.4 (12.1)/65.7 (11.6)	Ischemic and hemorrhage	16.8/16.5	Shoulder	HSP	NR	8.4/8.3 (severe)
9	Liu et al., 2015/China	60	NR	NR	NR	Knee	NR	NR	6.63/6.53 (moderate)
10	Ojala et al., 2022/Finland	17	55.8 (7.1)	Ischemic and hemorrhage	NR	NR	CPSP	5.5	5.2 (moderate)
11	Park et al., 2011/South Korea	40	64.3 (11.1)/62.5 (12.2)	Ischemic and hemorrhage	±6 months	Shoulder	HSP	NR	6.7/6.9 (moderate)
12	Saha et al., 2021/India	30	57.4 (4.9)/59.7 (6.1)	Ischemic and hemorrhage	13.3/13.5	Upper limb	CRPS	NR	6.0/6.6 (moderate)
13	Zhao et al., 2021/China	38	30–59	Ischemic and hemorrhage	2 weeks–5 months	Upper and lower limb, and hemibody with and without face	CPSP	2–10 days	5.2/5.3 (moderate)
14	Zheng et al., 2018/China	178	53.6 (3.3)/54.3 (3.2)	NR	42 days/41 days	Upper limb	CRPS	NR	6.3/6.6 (moderate)

(Continues)

TABLE 1 (Continued)

No.	Citation/country	Intervention characteristics					Scale(s)
		Intervention group	Type of interventions	Control group	Duration	Follow-up outcomes	
1	Bae et al., 2014/South Korea	tDCS	NIBS	Sham-tDCS	3 weeks	Baseline, immediate post-intervention, post 1 week, and post 3 weeks	VAS
2	Choi and Chang, 2017/South Korea	rTMS	NIBS	Sham simulation	2 weeks	Baseline, day 1 post-intervention, post 1 week, post 2 weeks, and post 4 weeks	NRS
3	de la Cruz, 2020/Spain	Aquatic Ai Chi therapy + hydrotherapy and dry land	Aquatic therapy	Dry land therapy	12 weeks	Baseline, immediate post-intervention, and post 1 month	VAS
4	de Oliveira et al., 2014/Brazil	rTMS	NIBS	Sham-rTMS	10 days	Baseline and post-intervention	VAS
5	Fan et al., 2012/China	Acupuncture	Acupuncture	Western medicine	NR	Baseline and post-intervention	VAS
6	Gwak et al., 2009/South Korea	Bee venom acupuncture	Acupuncture	Normal saline	3 weeks	Baseline, post-intervention, and post 2 weeks	VAS
7	Ko et al., 2007/South Korea	Bee venom acupuncture	Acupuncture	Placebo	2 weeks	Baseline and post-intervention	VAS
8	Korkmaz et al., 2022/Turkey	High-intensity laser therapy + rehabilitation training	Laser therapy	Rehabilitation training	3 weeks	Baseline and post-intervention	VAS
9	Liu et al., 2015/China	Four knee acupoints	Acupuncture	Chinese herb	NR	Baseline and post-intervention	VAS
10	Ojala et al., 2022/Finland	rTMS	NIBS	Sham-rTMS	2 weeks	Baseline and post-intervention	NRS
11	Park et al., 2011/South Korea	Bee venom acupuncture	Acupuncture	Normal saline	4 weeks	Baseline, week 2, and post week 4	VAS
12	Saha et al., 2021/India	Mirror therapy + rehabilitation training	Mirror therapy	Rehabilitation training	4 weeks	Baseline, post-intervention, and post 2 weeks	NPRS
13	Zhao et al., 2021/China	rTMS	NIBS	Sham-rTMS	3 weeks	Baseline, day 3, week 1, week 2, and week 3	NRS
14	Zheng et al., 2018/China	Acupuncture + rehabilitation training	Acupuncture	Rehabilitation training	4 weeks	Baseline and post-intervention	VAS

Abbreviations: C, Control; CPSP, Central Post-Stroke Pain; CRPS, Pos-tstroke complex regional pain syndrome; HSP, Hemiplegic Shoulder Pain; I, Intervention; NIBS, Non-Invasive Brain Stimulation; NPRS, Numeric Pain Rating Scale; NR, Not Reported; NRS, Numeric Rating Scale; rTMS, repetitive Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation; VAS, Visual Analog Scale.

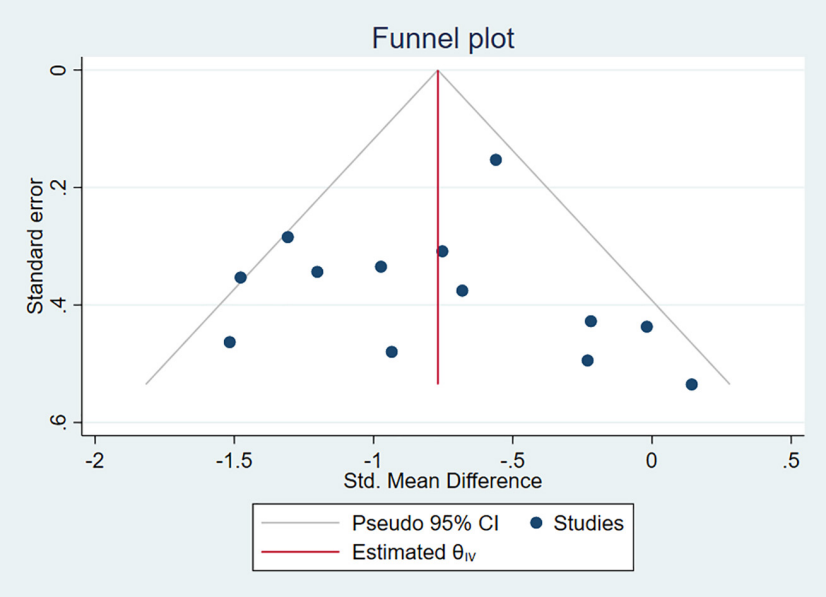


FIGURE 2 Funnel plot of effect of non-pharmacological interventions for post-stroke pain.

Pairwise meta-analysis

Overall effect immediately after intervention

Thirteen trials with a total of 552 post-stroke patients were aggregated to measure the overall score of pain immediately after intervention. The pooled SMDs were −0.79 (95% CI −1.06 to −0.53, $p < 0.001$, Figure 3a), demonstrating that non-pharmacological interventions resulted in a substantial reduction in the overall pain score compared to those received sham stimulation, western medicine, normal saline, placebo, and Chinese herb. The pooled analysis revealed moderate heterogeneity ($Q = 22.89$, $df = 12$, $I^2 = 47.58\%$).

Subgroup analysis

Effects based on intervention type

The pooled standardized mean differences (SMDs) for pain, assessed based on intervention modalities, were −0.78 (95% confidence interval [CI] −1.07 to −0.49) for acupuncture ($n = 6$) and −0.61 (95% CI −1.20 to 0.05) for non-invasive brain stimulation ($n = 5$ studies). This indicates that patients who received acupuncture experienced a significant reduction in pain (see Figure 3b).

Effects based on post-stroke pain type

The pooled standardized mean differences (SMDs) were calculated for central post-stroke pain ($n = 5$) and hemiplegic shoulder pain ($n = 4$ studies), and other pain types ($n = 3$) were −0.51 (95% CI −1.06 to 0.05), −1.11 (95% CI −1.48 to −0.75), and −0.74 (95% CI −1.01 to −0.47), respectively, indicating that the intervention group experienced a substantial reduction in hemiplegic shoulder pain and other pain types such as thalamic pain and complex regional pain syndrome; however, those with central post-stroke pain experienced no reduction (see Figure 3c).

Effects based on pain intensity

The pooled SMDs for moderate ($n = 12$) and severe post-stroke pain ($n = 2$ studies) were −0.88 (95% CI −1.22 to −0.55) and −0.87 (95% CI −2.10 to 0.36), demonstrating that the intervention considerably reduced moderate post-stroke pain while having no impact on severe pain (see Figure 3d).

Effects based on intervention duration

The pooled standardized mean differences (SMDs) for interventions administered for less than 4 weeks ($n = 8$ studies) and for more than 4 weeks ($n = 4$) were −0.80 (95% CI −1.22 to −0.38) and −1.11 (95% CI −1.82 to −0.39), respectively, demonstrating that both intervention duration significantly reduced post-stroke pain (see Figure 3e).

Effects based on post-intervention evaluation

The pooled standardized mean differences (SMDs) for outcome follow-ups of less than 4 weeks ($n = 3$ studies) and of 4 weeks ($n = 3$ studies) were −1.05 (95% CI −1.58 to −0.53) and −1.93 (95% CI −2.95 to −0.92), showing that both follow-up durations significantly decreased post-stroke pain (Figure 3f).

Sensitivity analysis

The meta-leave-one-out analysis revealed that excluding each trial from the analysis had no influence on the overall stability SMDs of the outcome ($p < 0.001$) (see Figure 4).

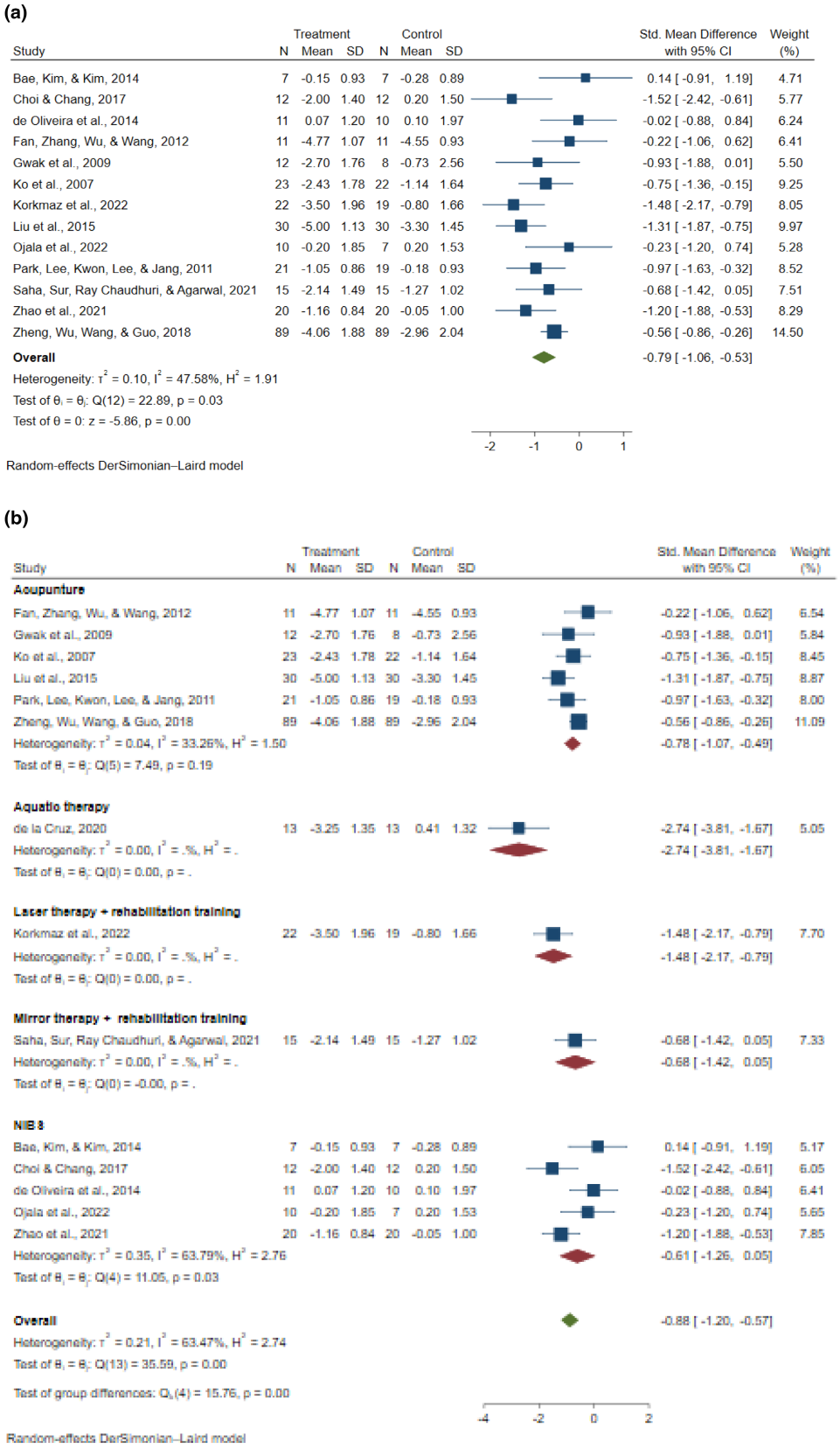
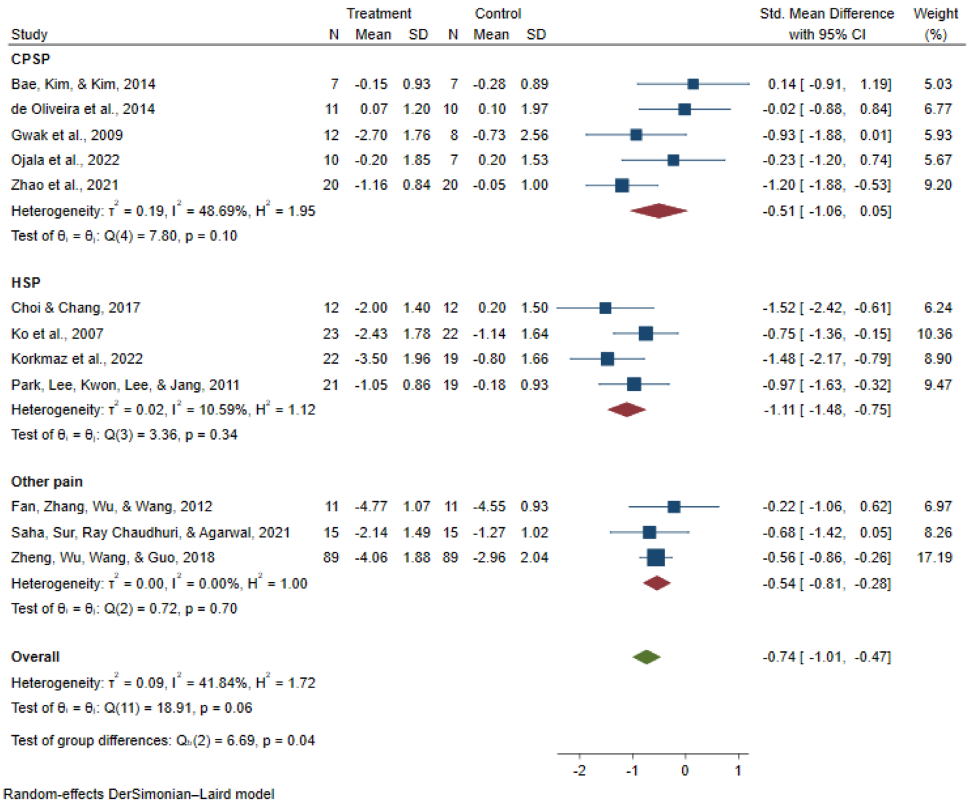


FIGURE 3 Forest plot of effect of non-pharmacological interventions for post-stroke pain. Forest plot of effect of non-pharmacological interventions for post-stroke pain. (a) Overall effect immediate post-intervention. Subgroup analysis: effect based on (b) the type of interventions delivered; (c) the type of post-stroke pain; (d) the type of pain intensity; (e) the duration of interventions delivered; (f) post-intervention evaluation.

(c)



(d)

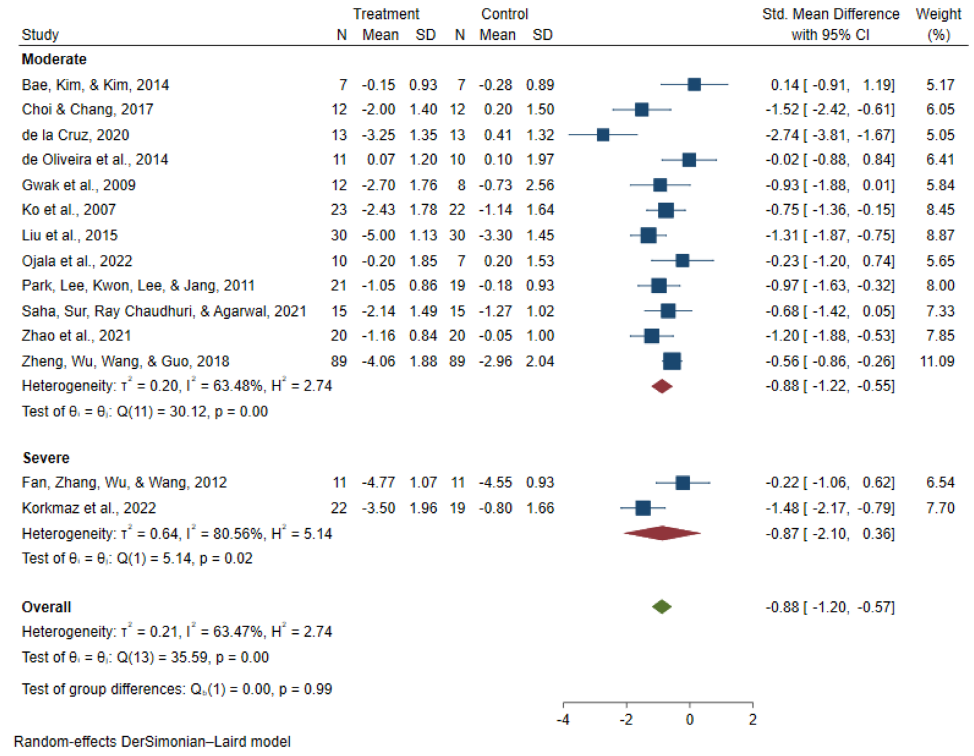


FIGURE 3 (Continued)

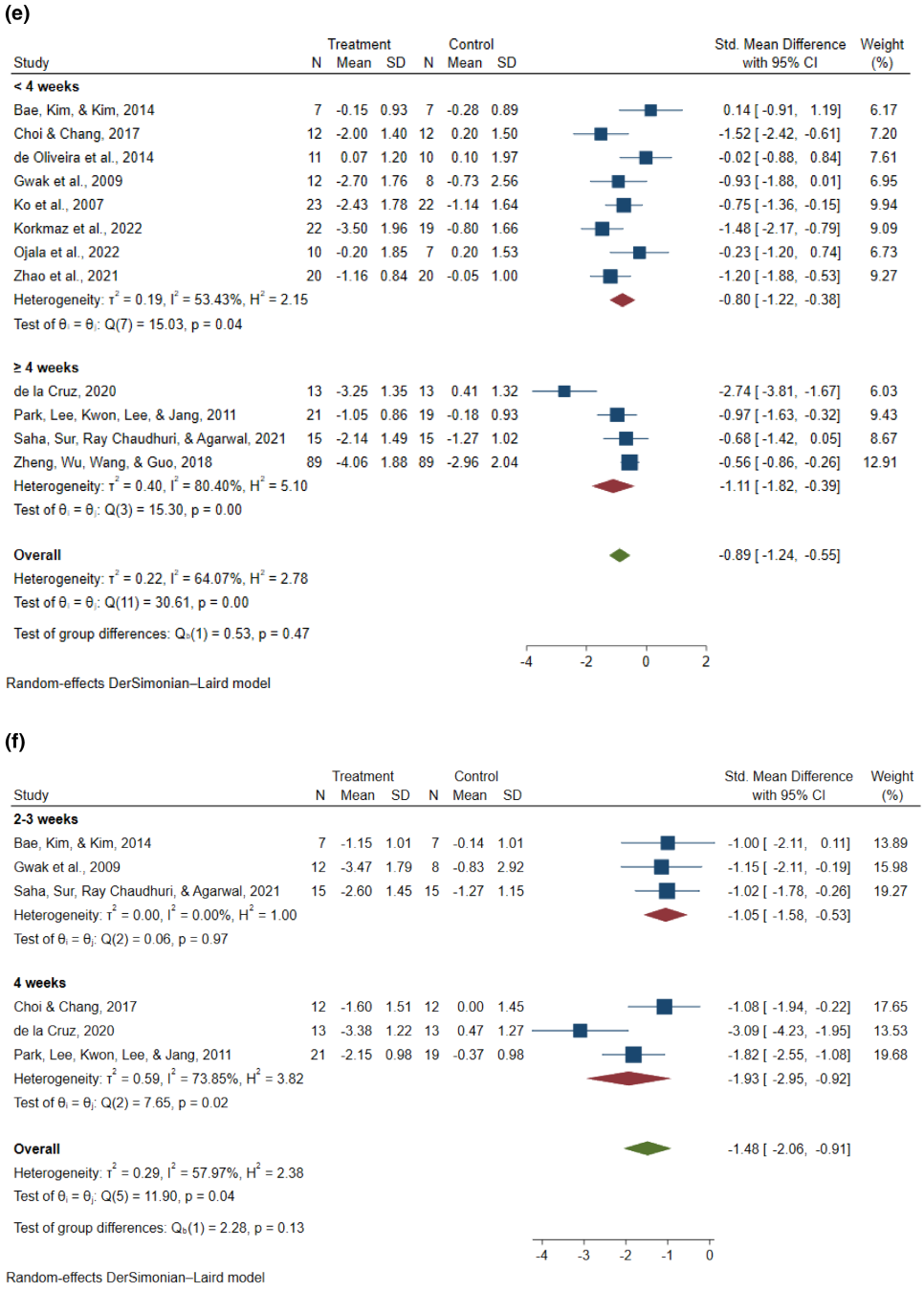


FIGURE 3 (Continued)

DISCUSSION

Although a previous review explored non-pharmacological interventions for pain in the stroke population, no meta-analysis has been conducted to date. New evidence has emerged from the present study further exploring the effectiveness of non-pharmacological interventions on pain after stroke. The pooled analysis demonstrated the beneficial effects of non-pharmacological interventions in reducing post-stroke pain. Subgroup analyses indicated that these interventions were effective in alleviating moderate post-stroke pain, administered for less than 4 weeks and for more than 4 weeks. Comprehensive investigation into the overall efficacy of non-pharmacological interventions and their specific impacts on post-stroke pain outcomes in diverse patient cohorts is warranted.

Among stroke survivors in a previous study, musculoskeletal pain appeared to be the most common symptom (in 72% of patients) and the second most prevalent was post-stroke pain syndromes, while the third was central post-stroke pain (Harrison & Field, 2015). In general, pain affects up to 30%–40% of stroke survivors (Paolucci et al., 2016). Central post-stroke pain is rarer: Its prevalence was 3.5% to 6.7% in a population-based study of people with post-stroke pain (Klit et al., 2011). Post-stroke pain is one

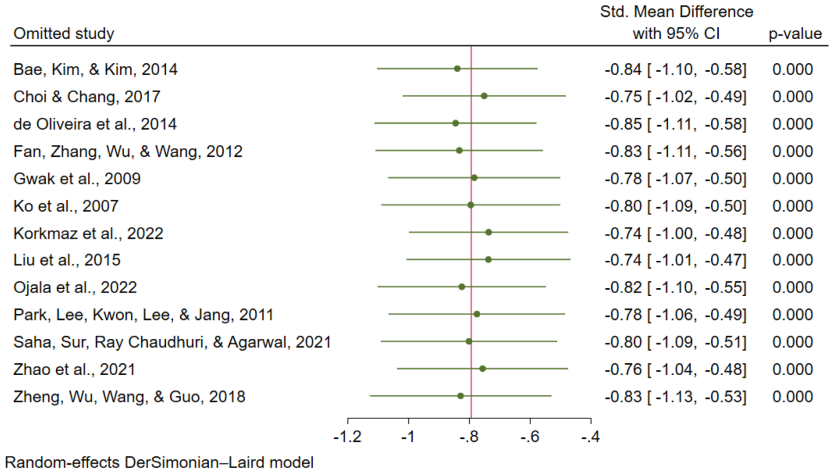


FIGURE 4 Leave-one-out meta-analysis.

of the most poorly understood complications. It impairs people's ability to manage daily living activities (Stewart et al., 2019) and causes fatigue (Su et al., 2020) and depression (Lee et al., 2021). A previous review narratively exploring pharmacological interventions for stroke survivors found that some medications reduced pain (Scuteri et al., 2020). The present study shows that non-pharmacological interventions can significantly reduce pain and would benefit stroke survivors by contributing to their pain management after stroke.

The results of the subgroup analysis indicate that acupuncture significantly reduces pain in patients after a stroke. Non-pharmacological interventions are effective in reducing post-stroke pain when implemented for less than 4 weeks or at 4 weeks. A significant reduction in post-stroke pain was also observed for at least two to 4 weeks after completing the intervention. The findings of the present study emphasize that the immediate benefits of non-pharmacological pain interventions need to be further quantified. Detailed quantification will help clinical decision-makers determine the best timing and integration of these therapies into stroke rehabilitation programs. This technique also offers to shed light on the possible long-term effects on pain management and overall patient outcomes. Researchers can influence future research objectives, healthcare policies, and guidelines in this domain by advancing quantitative methodologies aimed at optimizing the therapeutic efficacy of non-pharmacological therapies in controlling post-stroke pain.

In the present study, the effectiveness of non-pharmacological interventions depended on the type of post-stroke pain and pain intensity. A substantial pain reduction was shown in those with hemiplegic shoulder pain, thalamic pain, or complex regional pain syndrome; however, no pain reduction was observed in survivors with central post-stroke pain. There was also considerable pain reduction in stroke survivors with moderate pain. However, no similar impact was observed among those with severe pain. These non-significant effects underline the differences in the types of post-stroke pain that might occur between the acute and the chronic phase of stroke (Scuteri et al., 2020). This unresponsiveness of central post-stroke pain to both pharmacological and non-pharmacological pain interventions might be related to the persistence of binding in pain circuitry in the brain (Bae et al., 2014; Liampas et al., 2020). It suggests that a series of comprehensive therapeutic approaches is required to help central post-stroke pain patients and those with severe pain to cope with the pain burden.

Non-pharmacological interventions also did not have an overall significant impact on pain intensity. This finding highlights the subjective experience of pain which cannot be directly observed by those who are not experiencing it (Stilwell et al., 2022). Therefore, clinicians and researchers who have never experienced post-stroke pain may find it difficult to objectively observe, measure, and define the pain by words (Wideman et al., 2019). Furthermore, the present study did not find a change in post-stroke pain intensity after interventions in patients with severe pain and those with central post-stroke pain. These results might be related to the neurological damage caused by stroke not always being expressed in the behavior observed. However, behavioral disturbances caused by neurological conditions are common in those with severe pain (Saragih et al., 2022). This suggests that the severe pain of stroke survivors needs further investigation.

In the present study, the lower significance of pooled SMDs of pain intensity may be related to the high level of heterogeneity between the moderate (63.48%) and severe (80.56%) pain groups. The high heterogeneity in the meta-analysis was probably due to the clinical, methodological, or statistical origin of each of the studies (Melsen et al., 2014) or an insufficient number of studies with low risk of bias generally concealed in group allocation (Sun & Feng, 2019). A lack of blinding may bias the findings in favor of the intervention, leading to more exaggerated estimates of the intervention effects. Therefore, future randomized trials should consider blinding methods—whether the participants, interventionists who provided the treatments, or outcome assessors should be blinded.

Due to the dynamics of pain sensation following stroke, a multiple therapeutic approach combining pharmacological and non-pharmacological pain interventions seems crucial. The present

study obtained promising results for non-pharmacological pain interventions for the post-stroke population. Non-pharmacological pain interventions are urgently needed, particularly for post-stroke patients who experience adverse effects or contraindications of pharmacological interventions. Further research is necessary to understand whether combinations of pharmacological interventions and non-pharmacological pain interventions are associated with increased benefits compared to individual interventions. Tests should be conducted to determine which combinations and sequences of treatments are the most effective.

For interventions delivered over a minimum of two to four weeks, non-pharmacological approaches showed positive outcomes in reducing post-stroke pain among patients. However, considering that post-stroke pain can persist for more than three to six months, the effectiveness of extending these interventions beyond 4 weeks requires further investigation.

CONCLUSION

This study found that non-pharmacological pain interventions benefit patients after stroke. The evidence from this study contributes to an understanding of immediate post-stroke pain reduction after intervention, the type of intervention, duration of administration of the intervention, and post-intervention evaluation. Nevertheless, additional research is needed to explore the impacts of non-pharmacological interventions on the specific types and intensity levels of post-stroke pain. Furthermore, there is a need for further investigation into the effectiveness of interventions such as aquatic therapy, laser therapy, and mirror therapy in reducing post-stroke pain. Further randomized trials are also needed to investigate the effectiveness of non-pharmacological therapies in treating pain after stroke, particularly in patients with central post-stroke pain and stroke survivors with severe pain.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CLINICAL RESOURCES

- The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) PRISMA(prisma-statement.org).
- International Prospective Register of Systematic Reviews (PROSPERO) PROSPERO (york.ac.uk).
- Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1.

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