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STROKE (H.C. DIENER, SECTION EDITOR)

Updates in the Treatment of Post-Stroke Pain

Alyson R. Plecash[1] · Amokrane Chebini[1] · Alvin Ip[2] · Joshua J. Lai[1] · Andrew A. Mattar[1] · Jason Randhawa[1] · Thalia S. Field[1,3]

Abstract

Purpose of Review To provide an overview of the current treatment strategies for common subtypes of post-stroke pain.

Recent Findings There is growing research interest in non-pharmacological treatment approaches for chronic pain, including neurostimulation as well as lifestyle and psychosocial interventions. Newer pharmacotherapy research includes cannabinoids and NMDA-receptor antagonists as well as bee venom. Persistent post-stroke headache is an increasingly appreciated entity, though the role of novel chronic migraine treatments for post-stroke headache is not known.

Summary Overall, most treatment approaches to post-stroke pain lack high-quality evidence. Stroke survivors are in need of effective treatments based on methodologically sound evidence. To address the interplay of clinical and psychosocial factors that contribute to post-stroke pain, it may be reasonable to adopt a multimodal treatment strategy incorporating both lifestyle interventions and conventional therapies.

Keywords Stroke · Pain · Therapy · Non-pharmacologic · Lifestyle · Headache · Spasticity

Introduction

Stroke is the commonest cause of adult-acquired disability and the second-leading cause of death worldwide [1]. Recent advances in the treatment of acute ischemic stroke, including mechanical thrombectomy and image-guided selection of candidates for reperfusion therapy, have led to lower rates of functional dependence and decreased post-stroke mortality [2, 3].

Despite improved rates of functional independence, even stroke survivors with "good" or "excellent" outcomes as per traditional clinical trial outcome measures such as the modified Rankin Scale continue to experience "invisible" complications, including post-stroke pain, mood issues, fatigue, and reduced quality of life [4]. These complications are frequent, affecting up to half of stroke survivors, and recognition and treatment of these issues may help to improve function and post-stroke quality of life.

Post-stroke pain in particular may affect up to 50% of stroke survivors, with the majority experiencing pain on a daily basis [4, 5]. Those developing a new chronic pain syndrome after stroke have a greater likelihood of functional dependence, cognitive decline, depression, and suicidality, with pain severity correlating with degree of cognitive impairment and depression [6–8].

There are multiple post-stroke pain syndromes that can occur alone or in combination, and mechanisms may include both neuropathic and nociceptive elements. A number of demographic and clinical characteristics are risk factors for post-stroke pain. Female sex is an independent risk factor for the development of a post-stroke pain syndrome [6]. Although older age at stroke onset is associated with the development of any pain syndrome, younger patients are at increased risk for central post-stroke pain in particular [6, 9]. Premorbid peripheral vascular disease and alcohol and statin use prior to stroke, as well as a history of depression, predict the likelihood for developing any post-stroke pain syndrome [4, 6]. Stroke-related factors associated with developing pain include ischemic stroke and thalamic or brainstem localization. Those who develop post-stroke spasticity, severe upper extremity

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✉ Thalia S. Field
thalia.field@ubc.ca

[1] Division of Neurology, Faculty of Medicine, University of British Columbia, S169-2211 Wesbrook Mall, Vancouver, BC V6T 2B5, Canada

[2] Division of Physical Medicine and Rehabilitation, University of British Columbia, Vancouver, BC, Canada

[3] Vancouver Stroke Program, Vancouver Coastal Health, Vancouver, BC, Canada

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weakness and sensory deficits are also at higher risk [4, 10]. While the role of psychosocial factors in the development and prognosis of post-stroke pain specifically is understudied, pre-stroke anxious personality traits and depressive symptoms are an overall predictor for chronic pain and post-stroke complications frequently co-occurring with pain, including depression, anxiety, and fatigue [11–13]. .Social supports are protective against chronic pain and predict post-stroke social participation [14–16]. (Fig. 1).

Early and effective treatment of chronic pain is associated with improved prognosis both with regards to pain control as well as quality of life. Approaches to the identification and assessment of post-stroke pain types have been addressed in previous reviews [4, 17•, 18–20]. Here, we provide an updated overview of pharmacological and non-pharmacological therapeutic approaches for common subtypes of post-stroke pain. Given the complex interrelation between medical and psychosocial aspects of post-stroke pain and other post-stroke complications, a multimodal strategy incorporating lifestyle-related interventions in addition to medical treatments may optimize prognosis with improved quality of life and social participation after stroke.

Lifestyle and Psychosocial Interventions for Post-Stroke Pain

Both single-strategy and multimodal lifestyle interventions related to exercise, mindfulness, diet, and social participation are active areas of study in stroke rehabilitation. However, post-stroke pain remains an under-researched outcome and further high-quality evidence, particularly for non-exercise interventions, is needed.

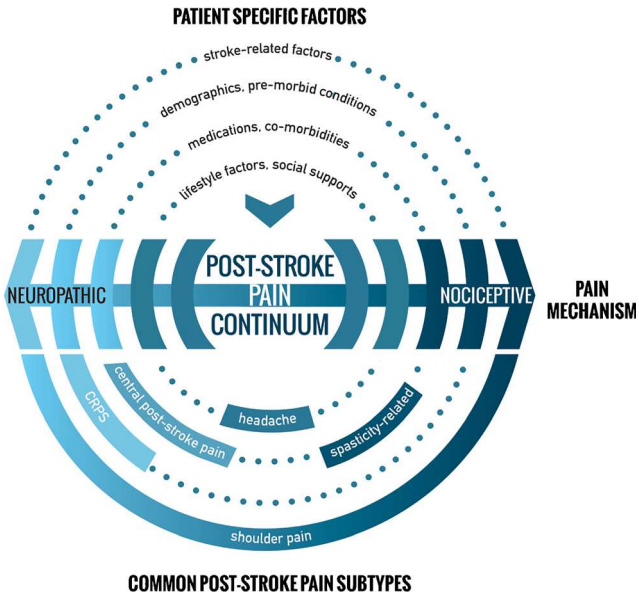

Fig. 1 Post-stroke pain continuum

The effects of exercise interventions specifically for post-stroke pain have not been studied extensively. However, exercise interventions in stroke survivors have shown to have a beneficial role in addressing challenges associated with pain after stroke, including mobility, fatigue, and self-efficacy [21, 22••]. In addition, exercise interventions provide opportunities for social participation and peer interactions, which are associated with improved self-management in chronic pain populations [23]. A qualitative instrumental case study design to evaluate a post-stroke peer support program found perceived benefits, including validation, hope and a reduced sense of isolation. This was true for both new stroke survivors and caregivers. Still, the authors concluded that further study was required to identify those most likely to benefit from individual as opposed to group programs, as well as to examine the durability of benefits over time [24]. To our knowledge, the role of online peer-support interventions has not been formally assessed.

Virtual reality (VR) and interactive video gaming have been studied for other forms of chronic pain, though evidence in support of their effectiveness in durable pain reduction is equivocal [25]. The role of VR and interactive gaming in stroke rehabilitation has been recently reviewed. While there is some evidence that these strategies may provide a benefit for upper limb function and activities of daily living over conventional rehabilitation, there was insufficient evidence to suggest a benefit in quality-of-life and pain was not studied as an outcome [26].

The effect of mindfulness on post-stroke rehabilitation outcomes was recently studied in a systematic review and meta-analysis. Pain was not specifically addressed, though the authors found a positive effect on sensorimotor outcomes [27]. A recent Cochrane review examining the specific benefits of yoga alone in chronic stroke cohorts found one of two included studies assessed pain, but found no benefit of an 8-week, twice-weekly intervention on the 3-item Pain-Enjoyment-General Activity (PEG) scale [28].

The overall evidence for post-stroke dietary interventions on clinical outcomes is scant. A subanalysis of the large randomized VITATOPS secondary prevention trial found a modest but significant effect on B-vitamin supplementation on post-stroke depression, though pain was not examined as an outcome [29].

Treatment Strategies for Specific Post-Stroke Pain Subtypes

Central Post-Stroke Pain (CPSP)

Central post-stroke pain broadly defines a chronic central pain disorder. The characteristics and patient descriptions of CPSP are variable, making it challenging to distinguish this entity

from other neuropathic pain conditions [10]. CPSP may be spontaneous (with constant and/or paroxysmal components) or can be evoked by nociceptive (hyperalgesia) or normioceptic (allodynia) stimuli. The reported prevalence of CPSP ranges from less than 1 to 35% of patients following stroke [30], and it is thought to account for roughly one-third of post-stroke pain [4]. Commonly, CPSP develops about 3 to 6 months after stroke; however, latencies ranging from within a week to several years following stroke are reported [30]. Possible mechanisms for this increasingly recognized, and perhaps heterogeneous, condition include central sensitization, alterations in spinothalamic function, disinhibition, and thalamic or other neuroanatomic changes [10].

Approach to Treatment: Pharmacologic

First-Line Therapies Treatment of CPSP is made challenging by the paucity of high-quality evidence to guide pharmacological management. A recent comprehensive systematic review on treatment of CPSP found low or very low-certainty evidence in favor of common treatment approaches recommended in international pain society guidelines, including tricyclic antidepressants and anticonvulsants [19].

Pharmacological approaches are extrapolated from other treatment models for neuropathic pain [19, 31]. Tricyclic antidepressants (e.g., nortriptyline and amitriptyline), serotonin and norepinephrine reuptake inhibitors (SNRI, e.g., duloxetine) or calcium channel α2δ ligands (e.g., pregabalin and gabapentin) are recommended as first-line agents for central post-stroke pain [32–36], though one randomized trial of a 13-week intervention of pregabalin (150–600 mg/day) versus placebo in 219 participants found no difference in pain as measured by the Daily Pain Rating Scale [33]. First-line agents have not been compared head-to-head in individuals with CPSP. A network meta-analysis of treatment approaches for chronic neuropathic pain, however, is currently underway [37].

Second- and Third-Line Therapies Antiepileptics, including carbamazepine or lamotrigine, may be used as second-line agents [38, 39]. Lamotrigine has better evidence in CPSP specifically, with one small placebo-controlled double-crossover trial of 30 patients finding a significant reduction in pain scores at 200 mg/day, but not at lower doses [40]. Neither carbemazepine nor levetiracetam were found to be effective in small randomized trials [41]. Evidence for third-line strategies, including ketamine [42], intravenous lidocaine infusions [43], or steroids [44, 45] in CPSP, is even more limited. These therapies are best provided by a dedicated pain specialist in collaboration with the treating neurologist in refractory cases.

Other Therapies and Opportunities for Future Research Clinicians are increasingly recognizing the utility of medications with N-methyl D-aspartate (NMDA) receptor antagonist effects (including ketamine, amantadine, memantine, other anti-epileptic medications, dextromethorphan, and methadone) for neuropathic pain [46]. Traditional opioids are generally not recommended as long-term strategies to treat neuropathic pain, given the potential for misuse and other adverse effects [47]. However, tramadol, which also has SNRI properties, may be an effective adjunct in patients who do not respond to the first-line medications for CPSP [48]. The current evidence for methadone in CPSP is limited [49]. Over-the-counter analgesics (non-steroidal anti-inflammatories, acetaminophen) are unlikely to offer significant benefit for neuropathic pain, aside from their potential to act as opioid-sparing agents [50].

Cannabis-based medications, such as nabilone, [51, 52•] are increasingly being used for chronic neuropathic pain and as an opioid-sparing strategy. A popular active area of research, cannabinoids are also being investigated for treatment of spasticity (see "Spasticity" section below).

Various topical medications (amitriptyline, ketamine, lidocaine, and capsaicin) are used in localized neuropathic pain, but have not been studied specifically in CPSP [53]. Given the reduced side effect profile of topical as compared with systemic therapies, this is an area that would benefit from future study.

Ultimately, combination therapies often offer the most benefit in CPSP. Many of these medications have synergistic mechanisms of action that may allow lower doses of individual agents to be used, thus improving tolerability and efficacy. A trial-and-error approach is usually required to achieve adequate pain control with tolerable side effects.

Neurostimulation

Invasive and non-invasive neurostimulation is an area of ongoing study for post-stroke pain, though the quality of evidence to date is limited by heterogenous protocols, small studies, and lack of randomized study design in many cases. The mechanisms by which motor cortex stimulation may modulate pain pathways invoke network-level activation of inhibitory and facilitatory circuits between interconnected neural structures and pathways [54••].

Non-invasive Brain Stimulation Non-invasive brain stimulation strategies, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are active areas of research for functional recovery after stroke [55, 56]. Similar to pharmacologic-related knowledge gaps in treatment of CPSP, regimen-specific factors, including anatomical targets for stimulation and optimal frequency and duration of treatment, are areas of uncertainty in need of further research. A recent systematic review found very low-quality evidence in favor of single-dose high-

frequency, but not low-frequency, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) for short-term effects on chronic pain of multiple etiologies [57].

Invasive Brain Stimulation There have been several non-randomized case series of electrical motor cortex stimulation including patients with CPSP [54••]. Two very small additional randomized studies for chronic neuropathic pain have compared on and off-stimulation conditions [58, 59]. A recent meta-analysis examining MCS for neuropathic pain of multiple etiologies found a pooled effect estimate of 35% improvement in visual analog pain scores in CPSP, though this was derived from only 58 individuals with CPSP overall across 12 studies [60].

A recent clinical trial examining deep brain stimulation (DBS) for CPSP used a randomized, placebo-controlled crossover design. Ten individuals with CPSP underwent bilateral DBS implantation targeting the ventral striatum and anterior limb of the internal capsule. There was no significant improvement in the primary endpoint, 6-month Pain Disability Index score. There were significant improvements in secondary outcomes related to the affective component of pain [61].

Spinal Cord Stimulation (SCS) fMRI and PET data have demonstrated that spinal cord stimulation (SCS) is associated with supraspinal functional alteration [54••]. Although SCS has documented evidence for treating particular types of peripheral neuropathic pain, there is no high-quality evidence supporting its effectiveness in CPSP [62]. The few uncontrolled published case series to date found success rates ranging from 7 to 75%, but possibly even higher rates of improvement with chronically implanted SCS [62–67]. Younger survivors and individuals with non-thalamic strokes were more likely to experience pain relief from SCS [62].

Other Therapies Caloric vestibular stimulation (CVS) was successful for treatment of CPSP in previous small case series [68–70]. A single-blind randomized pilot trial found that 3 weeks of twice-weekly bee venom acupuncture (BVA) point injections was associated with significant improvement in visual analogue pain scores as compared to saline injections in 16 patients with CPSP [71]. A recent Cochrane systematic review concluded that there is very low quality evidence supporting the use of transcutaneous electrical nerve stimulation (TENS) in patients with neuropathic pain, including CPSP [72].

Persistent Post-Stroke Headache

Persistent post-stroke headache has recently been defined as headache occurring around stroke onset that persists for more than three months [73]. Persistent post-stroke headache affects 23% of patients with risk factors including younger age, female sex, and presence of a pre-stroke primary headache disorder [74, 75]. In observational studies, persistent headache is especially prevalent in certain uncommon stroke mechanisms that typically present with acute headache, including cervical or intracranial artery dissection and cerebral venous sinus thrombosis [76, 77]. Spontaneous intracerebral hemorrhage, on the other hand, is associated with acute headache but has not been more strongly associated with persistent headache than atherosclerotic ischemic stroke [78]. Research to date on the prevalence of post-stroke headache includes methodological challenges such as a lack of distinction between survivors of ischemic and hemorrhagic stroke, and further high-quality studies are needed.

Clinical Assessment and Diagnosis In assessing patients with post-stroke headache, secondary causes of persistent headache including recurrent stroke, hemorrhage, cerebral venous thrombosis, dural arteriovenous fistula, dissection, pseudoaneurysm, posterior reversible leukoencephalopathy, reversible cerebral vasoconstriction syndrome, giant cell arteritis, and intracranial infection should be considered in the appropriate clinical context [17•]. Those with unexpected worsening of focal deficits or new focal deficits and headache warrant repeat neuroimaging. Consideration of further work-up in patients without focal deficits but with other headache red flags including thunderclap, positional, unremitting, or otherwise atypical headache syndromes is also important.

Co-morbid post-stroke complications including obstructive sleep apnea, musculoskeletal issues such as hemiplegic shoulder pain, altered biomechanics, uncontrolled hypertension, obesity, and polypharmacy are common generators of or contributors to persistent headache that should be screened for during assessment [17•]. Post-stroke fatigue and mood disorders can contribute to persistent headache and may need to be addressed to achieve the most robust effects of treatment.

Approach to Treatment No evidence-based guidelines for the management of persistent post-stroke headache exist [17•]. It may be reasonable to treat according to the most similar primary headache phenomenology, although this approach lacks evidence. Non-pharmacologic strategies that may be effective in other post stroke pain syndromes may also be effective for headache. These include exercise, stretching, physiotherapy, cognitive behavioral therapy (CBT), and biofeedback. These may be particularly important for patients for whom headache is part of a more widespread post-stroke pain syndrome, and patients with co-morbid depression, anxiety, or fatigue. Medication-overuse headaches may complicate any primary or secondary headache disorder and should be screened for at

stroke follow-up. Important considerations for post-stroke patients include avoidance of vasoactive agents.

Opportunities for Future Research There is limited clinical experience in persistent post stroke headache with the new calcitonin gene-related peptide (CGRP) antagonists for migraine. Stroke or vascular disease is not contraindications to the use of these agents by the US Food and Drug Administration or Health Canada labelling. Further phase 4 post-market data may clarify whether these agents should be trialed in this patient population. Use of other migraine prophylactic agents such as beta blockers, calcium channel blockers, antiepileptics, antidepressants, and nutraceuticals for persistent post-stroke headache with migrainous features may be warranted but should take stroke mechanism and comorbidities into account. There is a lack of evidence regarding strategies such as Onabotulinum toxin A or peripheral nerve blocks.

Spasticity

Spasticity is a velocity-dependent increase in muscle activation following a change in position/muscle length. Pathophysiologically, it is due to loss of descending inhibition on the spinal motor neurons from the injured upper motor neuron pathway. In the first month after stroke, 25–50% of patients are affected, with prevalence increasing over time [79–82]. .Risk factors for developing spasticity include stroke severity on baseline assessment, involvement of subcortical white matter tracts or the basal ganglia, and hemorrhagic stroke [82–84]. Spasticity is associated with post-stroke pain. A small prospective longitudinal study found that pain occurred in a majority of stroke survivors with spasticity (72%), but in only a minority of those without (1.5%) [79].

Approach to the Treatment of Post-Stroke Spasticity Traditionally, spasticity following stroke has been managed with splinting and range-of-motion exercises, despite challenges in tolerability/adherence, as well as an absence of evidence that these interventions are effective [85, 86]. To our knowledge, the effectiveness of splinting on reducing post-stroke pain has not been systematically studied.

Botulinum toxin injections have become a common treatment for spasticity. The effectiveness of botulinum in reducing spasticity in stroke patients is well-established [87, 88]. More recently, it has been shown that in addition to reducing spasticity, botulinum also reduces pain, and improves functionality at work for stroke patients [89].

Oral pharmacologic anti-spastic agents, including baclofen, tizanidine, diazepam, and dantrolene, are often used in spite of little evidence for their effectiveness in the post-stroke setting. A recent Cochrane review revealed insufficient evidence for spasticity reduction and functional improvement with the use of these agents in stroke populations [90]. Intrathecal and oral baclofen administration have been compared in a small randomized trial in a spinal cord injury population; the intrathecal group had reduced spasm frequency and severity, though there were no differences in pain or quality of life between groups [91]. One randomized trial comparing intrathecal baclofen to conventional medical management with oral antispastics was associated with improvement in both pain and spasticity in the baclofen group, though loss to follow-up and cross-over in a small trial make the conclusions more challenging to interpret [92].

Opportunities for Future Research There is increasing interest in the use of cannabinoids for treating spasticity. A recent meta-analysis [93] found efficacy for medical cannabinoids in the treatment of spasticity from multiple sclerosis (MS) and spinal cord injury, but not in stroke populations. The same review identified efficacy for the treatment of pain from multiple etiologies (neuropathic, MS-related, cancer and non-cancer, rheumatologic, etc.), but pain resulting from spasticity was not directly assessed. Recruitment is currently underway for a randomized trial comparing a cannabinoid (tetrahydrocannabinol and cannabidiol) oral spray to placebo for treatment of post-stroke spasticity, with pain as a secondary outcome [94].

Neuromodulatory transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are also being explored as therapies for spasticity. While there is some data for reduced post-stroke spasticity with TMS [95], the evidence to date does not support the routine use of non-invasive neuromodulation for spasticity [96].

Hemiplegic Shoulder Pain

Post-stroke shoulder pain is multifactorial, and both nociceptive and neuropathic mechanisms may contribute. It has been associated with shoulder soft tissue injury, as demonstrated by abnormal ultrasound findings of subacromial bursitis, bicipital tendinopathy, and rotator cuff pathologies commonly seen in patients with stroke [97, 98]. The altered movement patterns of patients at certain stages of motor recovery post-stroke have also been linked to shoulder pain, specifically glenohumeral subluxation in the acute phase and spasticity and adhesive capsulitis in the chronic phase [99, 100]. There is also mounting evidence for neuropathic pain mechanisms in chronic hemiplegic shoulder pain (HSP) as lower pain thresholds and higher rates of allodynia and hyperpathia have been demonstrated [101, 102].

The prevalence of shoulder pain following stroke was previously estimated to be 25–50% [4]. More recently, a retrospective study found a decreasing prevalence from 13% of

stroke rehabilitation inpatients in 2000 to 8% in 2015, which may be attributed in part to improvements in multidisciplinary acute care stroke units [103].

Clinical Assessment and Diagnosis Given the potential for multiple mechanisms contributing to HSP, with approximately one-third of HSP patients having two different shoulder pathologies, clinicians should conduct a thorough neuromusculoskeletal examination to evaluate for tone, strength, sensory changes, range of motion, joint alignment, and musculoskeletal pathologies [99, 104, 105]. If bony or soft tissue abnormalities in the shoulder are suspected, plain radiographs or ultrasound can be considered, respectively. The diagnosis of complex regional pain syndrome (CRPS) is based on the validated Budapest Criteria, but a triple phase bone scan can help exclude the disease [106, 107]. A diagnostic subacromial lidocaine injection test may assist in the differentiation between subacromial pathology and adhesive capsulitis [108].

Approach to the Treatment of Post-Stroke Shoulder Pain Treatment of post-stroke shoulder pain must be tailored based on clinical assessment and diagnoses. With pain and evidence of glenohumeral subluxation, the use of lap boards, arm troughs, shoulder orthoses, and neuromuscular electrical stimulation (NMES) should be considered. A recent systematic review found that shoulder orthoses reduce subluxation, but only while they are worn, and orthoses with both proximal and distal attachments were most effective [109]. Orthoses also improved pain, were well-tolerated, and did not increase the risk of contracture, spasticity, or hand edema [109]. No studies have tested whether immediate application of orthoses could prevent subluxation or pain, which represents a key question for future research [109]. Neuromuscular electrical stimulation (NMES) has been proposed to reduce subluxation by contracting and strengthening supraspinatus and posterior fibers of deltoid, which are important muscles for glenohumeral stabilization [110]. Two systematic reviews and meta-analyses reached similar conclusions: NMES was effective at reducing shoulder subluxation in the early post-stroke (less than 6 months), but not late post-stroke period, and did not improve shoulder pain or arm function [84, 111]. .Two randomized trials found that taping decreased shoulder pain but was ineffective in reducing subluxation [112, 113].

If the clinical examination of the patient with shoulder pain demonstrates spasticity, then strategies to manage spasticity should be employed (see "Spasticity" section above). Botulinum toxin can be injected into subscapularis and pectoralis major, which are the two most common spastic muscles implicated in HSP [114]. There are conflicting results from systematic reviews as to whether botulinum toxin injections help to improve post-stroke shoulder pain. A Cochrane systematic review found that a single intramuscular injection of botulinum toxin significantly reduced HSP at 3 and 6 months post-injection, though there were few studies and all were small [115]. A more recent systematic review and meta-analysis on the topic found a trend towards positive summary effect sizes for spasticity-related shoulder pain in the context of presumed insufficient statistical power [116]. There is a dearth of research into whether other spasticity interventions such as physiotherapy, pharmacotherapy, or phenol injections would be helpful for HSP.

Only a single small study...related to adhesive capsulitis. The investigators found that intraarticular steroid injection combined with hydrodilatation was better than conventional therapy or steroid injection alone in decreasing pain and improving shoulder range of motion and function [117]. The paucity of research in this common condition, implicated in one-half of post-stroke shoulder pain, is disappointing, and future studies should address this knowledge gap [105].

Treatment for post-stroke complex regional pain syndrome (CRPS) is better established in the literature, and includes early mobilization, mirror therapy, oral corticosteroids, stellate ganglion blockade, and psychological therapy [20, 114]. One small trial of 52 rehabilitation inpatients with subacute stroke and CRPS found that a 4-week upper extremity aerobic exercise program in combination with physiotherapy significantly improved pain and other symptoms of CRPS compared to physiotherapy alone [118]. A systematic review and meta-analysis of 38 studies concluded that adjunctive use of acupuncture with standard rehabilitation may be effective for improving pain, motor function, and performance of activities of daily living in patients with stroke [119]. Intravenous ketamine infusions were found to provide clinically meaningful pain relief of 3-month duration in patients with CRPS in a recent systematic review and meta-analysis, but no studies have specifically evaluated patients with post-stroke CRPS [120].

Finally, there is a limited but growing body of evidence for relatively new interventions in HSP. Bee venom interventions involve delivery via acupuncture needles or bee stingers to acupoints on the skin. Bee venom is thought to exert its therapeutic effects through anti-inflammatory, anti-apoptosis, and neuroprotective mechanisms [121]. A systematic review and meta-analysis of four small Korean trials suggested possible effectiveness of bee venom in treating post-stroke shoulder pain [122]. The suprascapular nerve has become another target for intervention in HSP because it receives sensory input from the shoulder joint and is implicated in sensitization related to chronic shoulder pain [123]. One randomized trial found that suprascapular nerve block significantly improved shoulder pain for up to 12 weeks compared to placebo injection [124], whereas two other trials demonstrated similar efficacy between suprascapular nerve block and intraarticular shoulder steroid injection in improving shoulder pain and passive range of motion [125, 126].

Recommendations for Future Research HSP is a common post-stroke pain syndrome and represents a challenge for both research scientists and clinicians. As it is known that multiple neurological and musculoskeletal pathologies can contribute to the broad diagnosis of HSP, we propose that improved differentiation of pain mechanisms, with associated accepted definitions (subluxation and adhesive capsulitis, for example, lack diagnostic criteria), are needed. The predominant underlying cause, or combination of causes, of HSP should be identified by thorough clinical assessment during study enrolment so that targeted interventions for subluxation-related pain, spasticity-related pain, and adhesive capsulitis-related pain can be better tailored to participants. In addition to small sample sizes, the heterogeneity of mechanisms for HSP in the existing literature may explain in part the conflicting and negative results in the existing literature on treatment of HSP.

Conclusions

Post-stroke pain is common and associated with impaired function and poorer quality of life in stroke survivors. However, its prevalence and natural history are understudied. Further, research focused on treatment of post-stroke pain is limited and the existing literature is frequently challenging to interpret due to methodological limitations. There is an urgent need for high-quality research on therapy for post-stroke pain (Table 1). In the interim, clinicians should actively inquire about pain in stroke survivors, even in those with a high level of functional independence, and should consider a multimodal approach to therapy incorporating lifestyle interventions in addition to pharmacological and non-pharmacological medical treatments.

Table 1 Suggestions to improve the methodological quality of research on post-stroke pain

Clarifying prevalence, risk factors, and prognosis
Inclusion of pain as a secondary outcome in acute and secondary prevention stroke trials
Use of common data elements for measurement of pain as well as potential contributing conditions (depression, fatigue, etc.)
Improving intervention studies
Improved homogeneity of participants by stroke mechanism, pain syndromes
Measurement and adjustment for potential demographic, clinical and psychosocial confounders
Use of defined and accepted criteria for pain syndromes
Large, multicenter randomized controlled trials, powered to detect clinically meaningful outcomes
Prospective design with adequate longitudinal follow-up
Minimization of loss to follow-up, cross-over

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Compliance with Ethical Standards

Conflict of Interest Alyson R. Plecash, Amokrane Chebini, Alvin Ip, Joshua J. Lai, Andrew A. Mattar, and Jason Randhawa each declare no potential conflicts of interest.

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- •• Of major importance

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