Vagus nerve stimulation to improve post-stroke motor function and activity (Review)

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ABSTRACT

Rationale After a stroke, many people experience persistent upper extremity (UE) motor impairments (that is, deficits in strength, coordination, and muscle tone), which can limit activities such as reaching, grasping, and manipulation. Despite conventional rehabilitation, recovery of UE function often remains limited. Vagus nerve stimulation (VNS), applied invasively or non-invasively (transcutaneously), has been proposed as an adjunct to rehabilitation to enhance neuroplasticity and improve motor outcomes after stroke. While early trials have reported mixed findings, the overall effectiveness and safety of VNS interventions in this context are uncertain.

Objectives To assess the potential benefits and harms of vagus nerve stimulation (VNS) as an add-on treatment to rehabilitate people who have post-stroke UE motor function impairments and activity limitations.

Search methods We searched for published trials in the Cochrane Library, MEDLINE, Embase, Scopus, PsycINFO, CINAHL and PEDro. We also handsearched for reference lists and looked for other relevant studies on Google Scholar. We performed the searches up to May 2025.

Eligibility criteria We included randomised controlled trials (RCTs) that assessed the effect of VNS paired with conventional rehabilitation, compared to conventional rehabilitation alone (or paired with sham VNS) in adults (≥ 18 years) with a first-ever ischaemic or haemorrhagic stroke, at any post-stroke phase.

Outcomes Our critical outcomes were UE motor function and the number of participants with at least one serious adverse event (SAE). Our main important outcomes were UE activity and quality of life.

Risk of bias Two review authors independently screened references, selected studies based on eligibility criteria, extracted data, and assessed the risk of bias in each included study using the Cochrane RoB 2 tool.

Synthesis methods When the studies were sufficiently similar, we synthesised VNS benefits and harms using a fixed-effects model meta-analysis for dichotomous outcomes and a random-effects model for continuous outcomes.

Included studies We included 10 studies with a total of 547 participants that met our inclusion criteria. The included studies took place in China, the UK, **t**he USA, and Italy. All studies were published in peer-reviewed journals. Nine were written in English, and one in Chinese. Three studies applied VNS invasively and seven non-invasively (transcutaneously). All interventions were paired with rehabilitation (motor training) and compared with rehabilitation alone. All studies included both men and women. Most treatments were given in outpatient hospital services or health centres. All studies measured outcomes at short-term (six to 12 weeks after treatment), three studies at medium-term (six months after treatment), and one study at long-term (12 months after treatment). We also identified 23 ongoing studies and 14 studies are awaiting classification.

Synthesis of results Compared with conventional rehabilitation alone, the evidence is very uncertain about the effect of VNS paired with rehabilitation on UE motor function in the short-term (SMD 1.22, 95% CI 0.68 to 1.77; 10 studies, 499 participants; very low-certainty evidence). VNS paired with rehabilitation may result in little to no increased risk of SAEs compared to rehabilitation alone (RR 2.38, 95% CI 0.77 to 7.30; 8 studies, 416 participants; low-certainty evidence). The evidence is very uncertain about the effect of VNS plus rehabilitation on UE activity (SMD 0.88, 95% CI -0.09 to 1.86; 6 studies; 186 participants; very low-certainty of evidence) and quality of life (SMD 0.04, 95% CI -0.30 to 0.37; 3 studies, 180 participants; very low-certainty of evidence) compared to rehabilitation alone in the short-

term. For the critical and main important outcomes, most studies had an overall high risk of bias. Few included studies took long-term follow-up measurements.

Authors' conclusions Comparing VNS paired with rehabilitation to rehabilitation alone, we found very uncertain evidence for the effects on UE motor function, UE activity, and quality of life in the short-term. VNS may result in little to no increased risk of SAEs. The body of evidence on the benefits and harms of VNS is limited by the risk of bias in the included studies, the small number of included studies, and the relatively small sample sizes.

PLAIN LANGUAGE SUMMARY

Is vagus nerve stimulation added to rehabilitation more effective than rehabilitation alone in the recovery of upper limb function and activity after stroke?

Key messages

• For people who have had a stroke, it is unclear whether vagus nerve stimulation (VNS) paired with rehabilitation is better than rehabilitation alone for improving shoulder, arm, forearm, wrist, and hand movement, and quality of life up to 3 months after treatment.

• VNS may result in little to no increased risk of unwanted effects. The included studies reported few unwanted effects, and none were clearly related to VNS treatment.

• This Cochrane review highlights research gaps, such as the lack of long-term follow-up after treatment. Some studies looked at quality of life but did not always report the results.

What is the vagus nerve?

The vagus nerve is a long nerve (a bundle of fibres like an electrical cable) that runs from the head into the body. It helps regulate essential body functions, such as heart rate, breathing, and digestion.

How might stimulation of the vagus nerve help people who have had a stroke?

During a stroke, blood flow to the brain is interrupted, causing brain cells to die. People who survive a stroke often have difficulty with movement. Their shoulders, arms, wrists, and hands (upper limbs) may not work properly due to reduced strength and co-ordination. This affects their ability to perform daily activities. Recovery of upper limb function after stroke may be slow or incomplete. In addition to normal rehabilitation treatments, such as medication and physiotherapy, stimulating the vagus nerve with an electrical signal (VNS) might improve communication between the brain and the body and help people recover their upper limb function. Electrical signals can be sent to the vagus nerve using a surgically implanted device (invasive VNS) or electrodes on the skin (non-invasive VNS). How VNS works is not fully understood, but may help by reducing inflammation and changing the activity of different body chemicals. Unwanted side effects of VNS may include hoarseness and numbness in the throat-chin area, shortness of breath, and slow heart rate. Also, there is risk of infection and bruising in people who have surgically implanted VNS.

What did we want to find out?

We wanted to find out if VNS alongside standard rehabilitation treatments helped people who had a stroke recover better upper limb function than by rehabilitation alone. Also, whether there were any unwanted effects and any effects on quality of life. We mainly looked at the effects of VNS 6 to 12 weeks after treatment.

What did we do?

We searched for studies that compared VNS paired with rehabilitation versus rehabilitation alone in people who had a stroke. People in the studies had to be 18 years or older, and could be at any stage of recovery from their first stroke. We checked the studies for quality, combined their results, and rated our confidence in the evidence based on their methods, size, and quality.

What did we find?

We found 10 studies that included 547 participants. The included studies took place in China, the UK, the USA, and Italy. Nine were written in English, and one in Chinese. All VNS treatments were paired with rehabilitation and compared with rehabilitation alone. Three studies used invasive VNS, and seven studies used non-invasive VNS. All studies included both men and women. Either outpatient hospital services or health centres treated most people. All studies measured results 6 to 12 weeks after treatment, three studies measured 6 months after treatment, and one study measured 12 months after treatment. We also found 23 ongoing studies, and 14 studies that are complete but their results are not yet available.

Main results

We are very uncertain about the effect of VNS paired with rehabilitation on upper limb movement (10 studies, 499 people), and quality of life (3 studies, 180 people) 6 to 12 weeks after treatment compared to rehabilitation alone. VNS may result in little to no increased risk of unwanted effects (8 studies, 416 people). This corresponds to about 42 out of 1000 people experiencing unwanted effects with VNS paired with rehabilitation compared with 19 out of 1000 people with rehabilitation alone.

What are the limitations of the evidence?

Our confidence in the results of this review is very low to low. Studies showed inconsistent results and included only small numbers of people. Studies were also quite different from each other as they used different types of VNS and different kinds of rehabilitation, which made it difficult to compare the results. While a few included studies were of good quality, others had problems with how they were planned and reported, which makes their results less trustworthy. Not all study results have been published yet. This Cochrane review highlights research gaps, such as the lack of long-term follow-up and lack of results that are important to people who have had a stroke. Some studies looked at quality of life but did not always report the results.

How up to date is this evidence?

The evidence is up to date to May 2025.

SUMMARY OF FINDINGS

Summary of findings 1. Vagus nerve stimulation (VNS) plus rehabilitation versus rehabilitation alone for participants with stroke

BACKGROUND

Description of the condition

Stroke is defined as "an episode of acute neurological dysfunction presumed to be caused by ischaemia or haemorrhage, persisting ≥ 24 h or until death [2, 3]". Stroke is the second-leading cause of death and the third-leading cause of disability worldwide [4]. People with hypertension (high blood pressure), cardiac diseases, diabetes, hypercholesterolaemia (high cholesterol), obesity, who smoke, consume excessive alcohol or drugs, and have a reduced level of physical activity face an increased risk of stroke [4]. Estimates from the Global Burden of Disease 2019 study indicate that one in four people will suffer a stroke during their lifetime [5]. Brain damage attributed to the loss of neurons caused by stroke can result in motor, sensory, and cognitive deficits. About half of the people who have had a stroke present with upper extremity (UE; i.e. shoulder, arm, elbow, forearm, wrist, and hand) motor impairment and cognitive disorders [6]. These disabilities may limit UE activity and functional independence, reduce quality of life, and affect mental health [7].

Description of the intervention and how it might work

Major international guidelines, including American, Canadian, and European guidelines, recommend exercise therapy programmes to improve post-stroke motor function [8, 9, 10, 11]. However, half of the people who receive rehabilitation will remain permanently impaired [12]. To promote recovery, interventions that enhance brain plasticity have been developed [13]. The improvement of brain plasticity, characterised by increased neural activity and connectivity, is an excellent predictor of motor recovery [14]. In this context, and to enhance outcomes of stroke rehabilitation, treatments involving vagus nerve stimulation (VNS) have recently been developed.

VNS

VNS involves any neuromodulation treatment that alters the activity of the vagus nerve, also known as the tenth cranial nerve. VNS typically involves surgical implementation of a pulse generator, leads, and electrodes under the skin of the left pectoral and neck regions while the person is under general anaesthesia [15]. This subcutaneous system is coupled with an external programmable device that serves to set up the parameters of the electrical stimulation [16]. Signal amplitude may vary from 0 to 3.5 mA, current frequency from 1 Hz to 30 Hz, and pulse width from 100 μs to 1000 μs [17]. When set up, the electrical signal is transmitted from the pulse generator to the vagus nerve through the leads [17]. VNS is generally regarded as safe and well tolerated. Adverse events (AEs), when they occur, are commonly associated with either the surgical procedure or the stimulation process itself. Aes related to stimulation include voice alteration, cough, dyspnoea (shortness of breath), paraesthesia (sensation of the skin that may feel like numbness (hypoesthesia), tingling, pricking, chilling, or burning), headache, and local pain [17]. With continued treatment, the frequency of these AEs tends to diminish.

More recently, studies have described the use of non-invasive (transcutaneous) VNS treatment, using a handheld stimulator over the skin covering the vagus nerve in the carotid triangle region [18], or in the auricular cavum conchae [19]. Like invasive VNS, non- invasive VNS is also considered safe and well tolerated, with skin irritation being the most prevalent AE [20]. Despite their shared goal of modulating vagus nerve activity, invasive and non-invasive VNS may differ in their mechanisms of action. While invasive VNS directly stimulates the vagus nerve through implanted electrodes, possibly allowing for precise modulation of its neural pathways, non-invasive VNS delivers stimulation through the skin, which may lead to less targeted vagal activation and potential engagement of other peripheral or cranial nerves [21, 22, 23]. Some studies report no effect on markers, such as the P3b event-related potential [24], which may suggest a lack of direct vagal activation. However, others demonstrate increased

salivary alpha-amylase [25], and transient pupil dilation, which potentially suggest more direct vagal activation [26].

Mechanism of action

Neuromodulatory networks

Overall, neurological recovery may be improved by enhancing the brain's ability to reorganise post-stroke residual networks (brain plasticity [27, 28, 29]). The biological rationale supporting the use of VNS to enhance neuroplasticity is derived primarily from preclinical studies and from human studies conducted in non-stroke populations [27, 30, 31, 32, 33, 34, 35]. While the precise mechanism of VNS remains unknown, preclinical evidence suggests that VNS may promote neuroplasticity by driving the rapid activation of neuromodulatory networks (cholinergic, serotoninergic, and noradrenergic systems), thanks to the nucleus tractus nerve solitarius projection of the vagus nerve [36]. Through this projection, VNS has been shown in animal models to modulate the release of serotonin, acetylcholine, and norepinephrine from the dorsal raphae nucleus, nucleus basalis, and locus coeruleus to different brain regions [34, 35]. Preclinical evidence suggests that the predominant mechanism may be cholinergic reinforcement. According to animal studies, the heightened noradrenergic activity induced by VNS is purported to influence the trisynaptic circuit in the hippocampus, a relay system involved in synaptic plasticity [30]. VNS-induced alterations in the locus coeruleus are closely tied to adrenergic signalling, and can potentiate perforant path-dentate gyrus-evoked potentials and enhance perforant path-CA3 field excitatory post-synaptic potentials [31]. This cascade of events is thought to be associated with long-term potentiation, a form of synaptic plasticity linked to enhanced learning and memory [37]. In animal models, VNS has been shown to increase the excitability and spontaneous spiking in the CA1 region and to enhance synaptic transmission [32].

Mediators

VNS may also induce lasting changes in synaptic plasticity by influencing mediators, such as growth factors, immediate early genes, and proteins critical for long-term potentiation [30]. This includes an increase in the expression of brain-derived neurotrophic factor (BDNF) and the activation of tropomyosin receptor kinase B, the receptor for BDNF [33]. Fibroblast growth factor expression may also be augmented by VNS, along with enhanced expression of adrenergic receptors and proteins crucial for long-term potentiation, such as GluN2B (N-methyl-D-aspartate (NMDA) receptor subunit) and its downstream signalling target calcium/calmodulin-dependent protein kinase II [30]. These comprehensive changes induced by VNS, reported mainly in preclinical animal studies, may contribute to long-term alterations in plasticity and memory consolidation in the hippocampus, highlighting the hypothesised multifaceted mechanisms through which VNS may enhance cortical reorganisation. The activation of neuromodulatory networks through the vagus nerve has been observed in experimental models to have neuroprotective effects, as it limits oxidative stress and neuroinflammatory activation, and enhances cortical map reorganisation by strengthening synapse efficacy and triggering neurogenesis [27, 36]. However, the extent to which these mechanisms translate to people with stroke remains uncertain.

VNS and stroke

Existing literature indicates that VNS can enhance hippocampal synaptic plasticity in healthy individuals, with possible improvements in attention and memory for people with epilepsy, when used as an antiepileptic intervention [30]. But there is currently no documented evidence that supports the efficacy of VNS in influencing neuroplasticity in people who have had a stroke. Nevertheless, animal studies support the positive effects of VNS on neuronal and corticospinal plasticity, therefore

underlining its potential to improve neurological recovery after a stroke [38, 39, 40]. These outcomes reinforce the perspective that VNS may be contingent on neuroplasticity, a phenomenon that unfolds over time and is sensitive to temporal dynamics. Therefore, we may expect differences between the effect of VNS during the acute and chronic phases of people with stroke. The purpose of starting in the acute phase is to prevent the loss of motor function or the development of other disabilities, by protecting the neurons from breaking down. Findings from animal models indicate that VNS may mitigate the AEs of spreading depolarisation waves in acute brain disorders [41, 42]. Therefore, VNS has been hypothesised to have the potential to preserve the penumbra and restrict the extent of the infarct core in people with acute stroke [43, 44, 45]. However, direct clinical evidence supporting this mechanism in humans is currently limited. During the chronic phase, the treatment goal is to promote neuroplasticity and induce neurogenesis to improve disabilities. A study conducted with rats with chronic stroke showed that VNS did not diminish the size of the lesion, but improved the recovery process by enhancing neuroplasticity [46].

VNS and mood

The positive effects of VNS on mood may also play a role in the context of stroke rehabilitation. Prior research indicated that mood symptoms following an acute stroke were correlated with a lower quality of life at one year, and that depressive symptoms may exert a pronounced influence on functional recovery [47]. In this context, the mood-enhancing benefits of VNS could plausibly contribute to an improved quality of life, and potentially, to better functional recovery. However, evidence directly supporting such effects in people with stroke is currently limited. When combined with motor training, animal studies reveal that VNS results in the reorganisation of cortical motor maps, affirming the capacity of VNS to foster synaptic plasticity when a targeted timing approach is used [48]. In adults with stroke, the combination of VNS and high-repetition, functional, and progressive exercise therapy showed promising results for UE motor function [49]. A pivotal randomised sham-controlled trial, including 108 people with ischaemic stroke, showed that VNS paired with rehabilitation improved UE motor control and activity [49]. These changes were maintained for three months post-intervention. The number of people achieving clinically important improvement in UE control was greater in the VNS group than in the control group.

Why it is important to do this review

Potentially, VNS may be an adjunctive treatment for UE rehabilitation in people who have had a stroke. Therefore, it remains important to assess the safety and effectiveness of VNS to improve post-stroke UE motor function and activity, to aid future guidance for VNS implementation in people who survive a stroke. Several meta-analyses have reviewed the effectiveness and safety of VNS in people after a stroke. However, not all of them used a GRADE approach to assess the certainty of the body of evidence [50, 51, 52, 53, 54, 55, 56]. Moreover, distinguishing between invasive and non-invasive VNS might be important. Non-invasive VNS may not be specific to the vagus nerve alone, potentially affecting other peripheral and cranial nerves. Also, it may induce reduced vagal activation compared to invasive VNS, which is designed to the regulatory standard [21, 22, 23]. Since the publication of Wei's meta-analysis [56], three new randomised controlled trials (RCTs) have been published that assessed the effect and safety of VNS in people with stroke [57, 58, 59]. These three studies enroled a total of 256 participants, which represents about 96% of the total sample size of Wei's meta-analysis [56]. All participants were treated during the subacute phase (compared to 85% of participants in previous studies [19, 49, 60, 61, 62, 63, 64]), and assessed participants with severe UE motor impairments.

Despite the findings of recent meta-analyses [50, 51, 52, 53, 54, 55, 56], several patient-related factors that potentially influence the effectiveness of VNS remain insufficiently understood, including

impairment severity and time since stroke onset. Some study authors also questioned whether motor changes induced by VNS could be clinically important [65]. If so, these therapies may also be used for other populations suffering from brain injury. To date, the distribution of VNS effects in the population and the implications for health equity remain under-explored. Due to the availability of new RCTs and the elaboration of subgroup analyses, it is worthwhile to synthesise the current evidence.

OBJECTIVES

To assess the potential benefits and harms of vagus nerve stimulation (VNS) as an add-on treatment to rehabilitate people who have post-stroke UE motor function impairments and activity limitations.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review [66], and PRISMA 2020 for the reporting [67]. We have reported deviations from the published Cochrane protocol in Supplementary material 8 [68].

Criteria for considering studies for this review

Types of studies

We only included RCTs, as they are the strongest study design to evaluate the efficacy of interventions [69]. We included parallel, cluster, and cross-over trials. We did not include quasi-RCTs.

Types of participants

We included studies reporting on adults (age > 18 years old) who were diagnosed with their first stroke (ischaemic or haemorrhagic), as defined by the American Heart Association [3]. We included participants who were in hyperacute (0 to 24 hours since stroke onset), acute (1 day to 7 days), early subacute (7 days to 3 months), late-subacute (3 months to 6 months), or chronic (> 6 months) phases [70].

We excluded studies of participants with mixed pathologies (for example, studies that involved adults with a stroke and adults with dementia).

Types of interventions

Experimental interventions

We included studies in which the experimental group received a VNS intervention, paired with usual care (as defined by the study authors) or conventional rehabilitation (intervention during which a clinician provides and supervises the rehabilitation tasks; therapy recommended by the most recent guidelines). In this Cochrane review, we considered a VNS intervention to be any technique involving the use of a device with either an invasive (placed under) or non-invasive (over the skin) placement to stimulate the vagus nerve with pulses of electrical energy. The signal amplitude of VNS usually varies from 0 to 3.5 mA, the current frequency from 1 Hz to 30 Hz, and the pulse width from 100 μs to 1000 μs. We considered all VNS interventions, regardless of their signal amplitude, current frequency, or pulse width. There were no restrictions on treatment intensity, duration and number of sessions, or length and frequency of treatment, for any VNS. We considered all types of coupling between VNS and motor training (VNS provided before, during, or after the trials).

Control interventions

We included studies in which the control group received usual care (as defined by the study authors), conventional rehabilitation, or another active intervention not involving neuromodulation that aims to promote the motor recovery and activity of the participant's affected limb (e.g. circuit training, virtual reality-based training, strengthening exercises). We also included studies in which the control group received sham VNS, minimal VNS stimulation (maximum of one pulse greater than 0 mA per session) or a brief series of stimulations with gradually decreasing intensities before the session (to enhance the masking of treatment allocation). There were no restrictions on treatment intensity, duration and number of sessions, or length and frequency of treatment for the control interventions. We considered all types of coupling between sham VNS and motor training (sham VNS provided before, during, or after

the trials).

Outcome measures

We included eligible studies that reported at least one of the following critical or important outcome measures.

Timing of outcome assessment

We considered the short-term, medium-term, and long-term time points for the analysis of critical and important outcomes.

• Short-term (post-intervention outcome is closest to six weeks but does not exceed 12 weeks). We used the short-term time point as the primary time point of interest.

• Medium-term (outcome closest to six months)

• Long-term (outcome closest to 12 months)

When trial authors did not distinguish between SAEs occurring between short-term and medium-term time points, we reported the results at the end of treatment.

Critical outcomes

Effectiveness of VNS

• UE motor function: Upper Extremity Fugl-Meyer Assessment (UE-FMA), a scale ranging from 0 to 66 points, with a minimal important difference (MID) of 6.6 points [71]

Safety of VNS

• Number of participants with at least one serious adverse event (SAE): measured at the end of intervention and follow-up; an SAE is any event that results in death, is life-threatening, requires or prolongs hospitalisation, leads to important or permanent disability, or causes congenital anomalies or birth defects [72]. We considered events such as infection, dysphagia (difficulty in swallowing), and vocal cord paresis (vocal cord weakness) as SAEs.

Important outcomes

Effectiveness of VNS

For studies using more than one scale to measure a given outcome, we used a hierarchical order of preference as recommended in the guidelines [73, 74, 75, 76, 77, 78]. We present the prioritised scales first. The others are enclosed in parentheses and listed in order of preference.

• UE activity: Action Research Arm Test (ARAT), a scale ranging from 0 to 57 points, with an MID of 5.5 points [79]; (Wolf Motor Function Test, a scale ranging from 0 to 5 points, with an MID of 0.4 points [80, 81])

• Spasticity: modified Ashworth Scale, a scale ranging from 0 to 4 points [82]; (modified Tardieu Scale, a scale ranging from 0 to 4 points for each joint [83]; UE Brunnstorm stage, a scale ranging from 1 to 7 points [84])

• Manual dexterity: Box and Block Test, a functional measure ranging from 0 to 150 points [85]; (Nine-Hole Peg Test, an average time measure ranging from 0 to 300 seconds [86])

• Lower extremity motor function: Lower-Extremity Fugl-Meyer Assessment (LL-FMA), a scale ranging from 0 to 34 points [71]

• Quality of life: Stroke Impact Scale (SIS), a scale ranging from 0% to 100% [87]; (EuroQol 5-dimension 5-level, a multidimensional scale [88])

• Anxiety: Hospital Anxiety and Depression Scale (HADS), a scale ranging from 0 to 21 points [89]; (General Anxiety Disorder scale, a scale ranging from 0 to 21 points [90])

• Stroke severity improvement: National Institute of Health Stroke Scale (NIHSS), a scale ranging from 0 to 42 [91]

• Relative infarct growth: a magnetic resonance imaging (MRI) measure based on diffusion-weighted imaging and computed as: (post-intervention lesion volume-baseline lesion volume/baseline lesion volume) × 100 [18, 92]

Safety of VNS

• Number of participants who discontinued the intervention (due to any reason related to the intervention)

• Number of participants with at least one AE: AEs included pain, fall, and injury.

Search methods for identification of studies

Electronic searches

We searched for published trials in the following databases:

• Cochrane Central Register of Controlled Trials (CENTRAL; 2025, Issue 4) in the Cochrane Library (searched 07 May 2025)

• MEDLINE via PubMed (National Library of Medicine) (1971 to 07 May 2025)

• Embase via Embase.com (Elsevier) (2007 to 07 May 2025)

• Scopus via Scopus.com (Elsevier) (2004 to 07 May 2025)

• PsycINFO via Ovid (1967 to 07 May 2025)

• CINAHL via EBSCO (1977 to 07 May 2025)

• PEDro via PEDro.org.au (1999 to 07 May 2025)

We developed a systematic search strategy for PubMed using MeSH terms and free terms. We then adapted this systematic search strategy for the other databases. All search strategies are presented in Supplementary material 1. We did not restrict the searches by language or article type [93].

Searching other resources

We searched for ongoing and unpublished trials in the following trial registry platforms:

• Open Grey (opengrey.eu)

• ClinicalTrials.gov (clinicaltrial.gov)

• World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx).

We handsearched the reference lists of all included studies, relevant scoping and systematic reviews identified during the searches, and conference papers (Conference Proceedings Citation Index- Science;

1990 to current) covering the use of VNS for stroke rehabilitation [93]. We also contacted trial authors of the included studies to request information about ongoing or unpublished studies.

We also performed searches on Google Scholar for studies that we could have missed or that were not published in the above-mentioned databases. We limited our screening to the first 30 pages of results (using the keywords 'vagus nerve stimulation', 'VNS', and 'stroke'; no filters applied).

We searched for retractions or errata notices for our included studies in the Retraction Watch Database (https:// retractiondatabase.org/RetractionSearch.aspx?) and in PubMed on 02 July 2025.

Data collection and analysis

One review author (JD) was an investigator in some of the included studies. Therefore, his contribution was limited to assessing the content of the manuscript and providing input on the Cochrane protocol [68], without influencing study selection, data extraction, analyses, risk of bias, or certainty of the evidence assessments.

Selection of studies

We downloaded all references from the searches and stored them in Covidence software [93, 94]. After removal of duplicates, two review authors (GE and IDS) independently screened the articles by their titles and abstracts. This process was followed by a meeting to resolve any conflicting selections between the review authors. If no agreement was reached, a third review author made the final decision (GEB). The review authors (GE and IDS) independently assessed the full text of all articles that were potentially eligible for inclusion. They met again to resolve any conflicting selections, and invited a third review author (GEB) in case of discrepancy. During the full-text assessment process, we compiled a list of studies excluded after full-text assessment. For each of these studies, we documented the primary reason for exclusion [93]. We also searched for potential errata statements of the included studies. Author retraction, fraud suspicion, or important limitations (calling into question the validity of the results) would have led to exclusion of the study [95].

Data extraction and management

Two review authors (GE and IDS) independently extracted the following data from each study, using a data collection form [95] (see Supplementary material 9). The two review authors (GE and IDS) pilot tested this form independently using a representative sample of the studies to be assessed.

For multi-arm studies, we only extracted data from relevant intervention groups [95]. For crossover trials, we only extracted data for the phase before crossover. Disagreements were resolved through discussion. One review author (GE) entered the data into Review Manager (RevMan) [96], and a second review author (IDS) checked that the data was entered correctly [96].

Risk of bias assessment in included studies

Two review authors (GE and IDS) independently evaluated the risk of bias in each included study using the Cochrane RoB 2 tool [97, 98]. This tool enables the assessment of risk of bias for each outcome. We evaluated the impact of assignment to the intervention for the short-term outcomes of the following outcome measures: UE motor function (assessed with the UE-FMA), UE activity (assessed with the ARAT and Wolf Motor Function Test), quality of life (assessed with the SIS), and SAEs. Domains covered by the risk of bias and initially proposed methods for cross-over and cluster RCTs are presented in Supplementary material 10.

For each domain, we classified the overall risk of bias for each outcome as either 'low', 'high', or 'some concerns'. In the case of uncertainty or disagreement between review authors, we involved a third review author (GEB); if needed, we contacted the study authors.

We used the Excel tool (available at riskofbiasinfo.org) to record and manage RoB 2 assessments. We then produced risk of bias graphs and risk of bias summary graphs. We provided support for the judgements and the sources of information for each risk of bias assessment [97].

Measures of treatment effect

We reported dichotomous outcomes, such as the number of dropouts, AEs, or SAEs using a risk ratio (RR) and 95% confidence interval (CI). For SAEs and AEs, we excluded from the meta-analysis any study reporting event counts without explicitly stating the number of participants experiencing at least one event.

For continuous outcomes, if the included studies used the same scale to measure the outcome, we reported the treatment effect using mean differences (MDs) and 95% CIs. If different scales were used to measure the same outcome, we measured treatment effectiveness by computing a standardised mean difference (SMD) and 95% CI [99]. For SMD, effect sizes were interpreted as small (≤ 0.2), moderate (0.2 to 0.8), or large (> 0.8) according to Cohen's convention [100]. When pooled SMD suggested a possible effect of VNS, we re-expressed SMDs as MDs in the units of a widely used scale to facilitate clinical interpretation [101]. More details are provided in Supplementary material 11.

We compared mean changes from baseline at the end of treatment, and at follow-up, as these data were available from most studies or could be imputed, instead of using post-intervention comparisons.

Unit of analysis issues

If individuals underwent more than one intervention (due to a cross-over design), we only included the data that were reported before the cross-over (first phase), since there is a risk of carryover due to the potential persistence of the effect of the first intervention [102]. For three-arm studies in which all intervention groups are relevant, we aimed to give priority to the splitting approach [103,104]. This method is detailed in Supplementary material 12.

While we did not use them as we did not include cluster-RCTs, we have provided the initially proposed methods for these types of RCTs in Supplementary material 13.

Dealing with missing data

In cases of missing data (either full-text report unavailability or missing statistical information), we contacted the corresponding authors of the included studies. For continuous data, if trial authors were unable to provide the mean and standard deviations (SDs), we converted the medians and their quartiles to means and SDs using Wan's approach [105]. Similarly, we converted CIs and standard errors of the means to SDs following the methods described in Chapter 7 of the Cochrane Handbook for Systematic Reviews of Interventions [97]. Where numerical data were unavailable, two review authors independently extracted data from published graphs using PlotDigitizer (version 3.1.6 2025) [106].

Reporting bias assessment

We evaluated reporting biases by comparing the information described in each trial's published protocol (in clinical trial registers) to the methods and results sections of the publication. We also used a funnel plot to check for small study effects, which may suggest publication bias (through symmetry visual analyses), if we found more than 10 studies that reported the same outcome. If we found asymmetry or

outliers (studies with markedly different intervention effect estimates), we undertook the Egger regression test to assess the influence of publication bias on each result [107].

Synthesis methods

If, based on the clinical heterogeneity assessment, the studies were sufficiently similar, we synthesised VNS treatment effectiveness for all critical and important outcomes using a meta-analysis. We used RevMan software for most statistical analyses [96]. We used a random-effects model, as we expected some heterogeneity between studies. Our detailed approach to managing outlying studies in cases of heterogeneity is presented in Supplementary material 14. We present the methods used to calculate Cis and prediction intervals (PIs) in Supplementary material 15. For dichotomous outcomes, in the case of rare events, we also conducted analyses in R [108], using a fixed-effects Mantel–Haenszel approach without continuity correction [109, 110]. If we included fewer than two studies, we summarised the results using a narrative synthesis (instead of a pooled statistical synthesis), in accordance with Synthesis Without Meta-analysis guidelines [111].

We quantified between-study statistical heterogeneity using the I^2 statistic. We interpreted it as either low (I^2 between 0% and 40%), moderate (I^2 between 40% and 60%), substantial (I^2 between 50% and 90%), or considerable (I^2 between 75% and 100%) [99, 110, 112]. We also assessed heterogeneity by visual inspection of forest plots, and with Chi^2 tests.

Investigation of heterogeneity and subgroup analysis

Post-lesional neuroplasticity is purported to be at its greatest within the first three months of brain injury. Therefore, we first aimed to start with subgroup analyses to compare the findings collected in the (hyper-)acute and early subacute phases (0 hours to 3 months post-stroke onset) with those collected in the late subacute and chronic phases (> 3 months post-stroke onset).

We also wanted to assess the influence of impairment severity (low-moderate (UE-FMA: 29 to 66) versus severe motor impairments (UE-FMA: 0 to 28)) [113] and VNS device set-up (invasive versus non-invasive) on post-stroke motor and activity outcomes.

Equity-related assessment

We aimed to assess health equity by exploring whether the VNS effect varied across population and context characteristics [104], including country income level (high-, middle-, and low-income countries [114, 115]) and sex (females, males) where data were available.

Sensitivity analysis

We initially aimed to conduct the following sensitivity analysis to assess the robustness of the decision we made in our analysis.

• Risk of bias: analyses limited to studies at low risk of bias and those with some concerns

• Imputation: analyses excluding studies with imputed data (such as estimated means and SD, or when data was extracted from plots)

• Dichotomous outcomes: analyses using alternative statistical methods for rare events, including the Mantel–Haenszel exact method and an inverse-variance random-effects model with Restricted Maximum-Likelihood estimator

• Outlying studies: analyses including outlying studies excluded from the primary analysis due to justified clinical diversity [110]

However, we did not perform these analyses when only a few studies were included, as they are not particularly informative, given that omitting a single study can disproportionately affect the results. Moreover, with only a few studies, such analyses could have been misleading, as they may have overstated the variability of findings rather than provided meaningful insights into the robustness of the results.

Certainty of the evidence assessment

We developed a summary of findings table for the following comparison.

• VNS paired with rehabilitation versus rehabilitation alone in people with stroke.

We included the following outcomes in the summary of findings table.

• UE motor function

• Number of participants with at least one SAE

• UE activity

• Quality of life

This summary of findings table comprises the population and settings, the experimental and comparison interventions, the four listed health outcomes, the measure of each outcome (RR, MD, or SMD), the magnitude of effect, the numbers of participants and studies, and the overall certainty of the body of evidence for each outcome [116]. We reported outcomes measured in the short-term (≤ 3 months).

Two review authors (GE and IDS) evaluated the certainty of the body of evidence for each outcome using the GRADE approach [116, 117]. GRADE rates the certainty of evidence for an outcome as either high, moderate, low, or very low, according to: study limitations/overall risk of bias, inconsistency, indirectness, imprecision, and publication bias [118]. We consulted a third review author (GEB) to address any disagreements, ultimately reaching a consensus.

We downgraded the certainty of the evidence by either one level for serious, or two levels for very serious, concerns for each domain. We provided more details in Supplementary material 16.

Consumer involvement

No consumer or patient involvement was incorporated in the design, conduct, or reporting of this Cochrane review.

RESULTS

Description of studies

Results of the search

As presented in Figure 1, we identified 3048 references after searching the different databases. A search of the trial registries elicited a further 165 records. After duplicate removal and title-abstract screening, we identified 122 references for full-tekst screening. After full-text assessment, we included 10 different RCTs (39 reports), and identified 23 ongoing studies (27 reports) and 14 studies (15 reports) awaiting classification (supposed to be completed, but not yet published).

Included studies

We included ten studies (Capone 2017 [119, 120, 121, 122]; Chang 2021 [123, 124]; Dawson 2016 [125, 126, 127, 128]; Dawson 2021 [129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142]; Kimberley 2018 [143, 144, 145, 146, 147, 148, 149, 150]; Li 2022 [151, 152]; Wang 2024 [59]; Wu 2020 [153, 154]; Zhang 2023 [58]; Zhang 2025 [57]), with a total of 547 participants that met our inclusion criteria. All the studies were published in peer-reviewed journals; nine were written in English and one in Chinese (Zhang 2023). An overview of synthesis and included studies is presented in Table 1.

We contacted the authors of six studies for additional information and received four responses (Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018).

Design

Nine included studies were two-arm RCTs, and one study was a three-arm RCT (Zhang 2023). Eight studies followed a parallel RCT design (Capone 2017; Chang 2021; Dawson 2016; Li 2022; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025), and two studies had a specific cross-over RCT design where only participants in the control group crossed-over (Dawson 2021; Kimberley 2018).

Setting

Five studies took place in China (Li 2022; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025), two in the UK and USA (Dawson 2021; Kimberley 2018), one in the UK only (Dawson 2016), one in the USA only (Chang 2021), and one in Italy (Capone 2017). Most interventions were delivered in outpatient hospital services or health centres. However, three studies required 24-hour hospitalisation following VNS device implementation (Dawson 2016; Dawson 2021; Kimberley 2018). Additionally, two of these studies included home-based delivery after in-clinic sessions (Dawson 2021; Kimberley 2018).

Participants

We have provided the demographic information of the included studies in Supplementary material 2. Sample sizes ranged from 14 to 124 participants. All studies included both men and women. Four studies explicitly mentioned pregnancy as an exclusion criterion (Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018). Across the included trials, the proportion of women ranged from 17% to 52%. All studies except two enroled a higher proportion of men than women (Chang 2021; Li 2022). All studies except one reported sex distribution by intervention and comparator groups (Chang 2021). Where available, the proportion of women ranged from 10% to 50% in the VNS groups and from 18% to 53% in the control groups. Mean ages across the study arms ranged from 53.7 to 69.2. Four studies included participants in the chronic phase (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021), one in both the late subacute and chronic phases (Kimberley 2018), one in the late subacute phase only (Zhang

2025), one in both the early and late subacute phases (Wang 2024), one in the early subacute phase only (Zhang 2023), and two in both the acute and early subacute phases (Li 2022; Wu 2020). Seven studies included participants with both ischaemic and haemorrhagic stroke, and three studies only included participants with ischaemic stroke (Dawson 2016; Dawson 2021; Wu 2020). Regarding the UE function, four studies used a threshold on the UE-FMA score as an inclusion criterion (Chang 2021; Dawson 2021; Kimberley 2018; Wang 2024), and one study used the ARAT (Dawson 2016). Baseline UE-FMA scores in the study arms ranged from 17.5 to 45.3. Further information about participants is presented in Supplementary material 17.

Interventions

The characteristics of the interventions are detailed in Supplementary material 2. Programme durations varied between 10 days and 18 weeks. Three studies used invasive VNS (Dawson 2016; Dawson 2021; Kimberley 2018), and seven used non-invasive (transcutaneous) VNS (Capone 2017; Chang 2021; Li 2022; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025). Five studies delivered VNS during an add-on session (Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018; Wang 2024), and before each add-on session in four studies (Capone 2017; Li 2022; Wu 2020; Zhang 2023). One study did not specify the timing of VNS delivery (Zhang 2025). Add-on sessions included UE robotic-assisted therapy (RAT) (Capone 2017; Chang 2021), functional UE motor training (Dawson 2016; Dawson 2021; Kimberley 2018; Wang 2024), or more general limbs and postural rehabilitation (Li 2022; Wu 2020; Zhang 2023; Zhang 2025). Participants exercised between 3 and 7 times per week, with a duration ranging from 30 minutes to 2 hours. Two studies delivered the intervention first in clinics and then at home (Dawson 2021; Kimberley 2018).

Control interventions included functional UE motor training provided alone (Dawson 2016), general limbs and postural rehabilitation provided alone (Zhang 2023; Zhang 2025), sham non- invasive VNS coupled with UE RAT (Capone 2017; Chang 2021), sham invasive VNS coupled with functional UE motor training (Dawson 2021; Kimberley 2018), sham non-invasive VNS coupled with functional UE motor training (Wang 2024), and sham non- invasive VNS coupled with more general limbs and postural rehabilitation (Li 2022; Wu 2020). In all included studies, the frequency of control interventions was matched with those of the experimental interventions.

Outcomes

Regarding critical outcomes, all studies measured UE motor function using the UE-FMA or its simplified version (Zhang 2025). Outcomes were measured at short-term in all studies, at medium- term in three studies (Dawson 2021; Kimberley 2018; Li 2022), and at long-term in one study (Li 2022). Although measured, only six studies provided post-intervention (and follow-up) mean scores and SD values (Capone 2017; Kimberley 2018; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025). All studies but one reported SAEs occurring between baseline and the end of the intervention (Zhang 2023).

Regarding important outcomes, one study measured UE activity using the ARAT (Wang 2024), and four studies used the Wolf Motor Function Test (Chang 2021; Kimberley 2018; Li 2022; Wu 2020). One study measured spasticity (Chang 2021), using the modified Tardieu Scale. Two studies assessed manual dexterity using the Box and Block Test (Kimberley 2018; Zhang 2023). One study measured LE motor function using the LL-FMA (Li 2022). Three studies assessed quality of life using the SIS (Dawson 2021; Kimberley 2018; Li 2022). One study measured anxiety using the HADS (Li 2022). Stroke severity, as measured by the NIHSS, was only used at baseline in one study (Capone 2017). One study determined relative infarct growth using the infarct volume (Dawson 2016), but only at baseline. All

studies reported the number of participants who discontinued the intervention, and all but one study reported the number of participants with at least one AE (Zhang 2023).

Ethics, funding, and conflicts of interest

All studies reported obtaining an ethical agreement. All but two studies listed sources of funding (Capone 2017; Zhang 2025). Funding was mainly provided through governmental and institutional research grants, with some studies also receiving support from medical device companies. Three studies declared potential conflicts of interest (Dawson 2016; Dawson 2021; Kimberley 2018).

Excluded studies

We excluded 34 studies after full-text assessment for the following reasons: study design (non-RCT) (10 studies), the intervention (e.g. not focusing on promoting motor function or no motor training as an add-on therapy) (17 studies), the comparison (e.g. active VNS or absence of motor training as an-add on therapy) (6 studies), and the population (included adults with multiple stroke) (one study). The full details are available in Supplementary material 3

Studies awaiting classification

Fourteen trials were supposed to be completed but are not yet published. These are summarised in Supplementary material 4.

We contacted the authors of these studies to request unpublished data, except for one study for which we could not identify any valid contact information [155]. When the review was submitted for editorial approval, one study author team had responded (ACTRN12623000376640 [156]), but we had not yet received the requested data.

Ongoing studies

Twenty-three ongoing RCTs are recorded and summarised in Supplementary material 5.

Risk of bias in included studies

Regarding the prespecified outcome of UE motor function (assessed with the UE-FMA), we assessed the risk of bias in all included studies. One study was at low risk of bias (Dawson 2021), three had some concerns (Dawson 2016; Kimberley 2018; Wu 2020), and six were at high risk of bias (Capone 2017; Chang 2021; Li 2022; Wang 2024; Zhang 2023; Zhang 2025).

We assessed the risk of bias for SAEs in all but one study (Zhang 2023). Four studies had some concerns (Dawson 2016; Dawson 2021; Kimberley 2018; Wu 2020), and five were at high risk of bias (Chang 2021; Capone 2017; Li 2022; Wang 2024; Zhang 2025).

We assessed the risk of bias for UE activity (assessed with the ARAT and Wolf Motor Function Test) in six studies (Chang 2021; Kimberley 2018; Li 2022; Wu 2020; Dawson 2016; Wang 2024). Three had some concerns (Dawson 2016; Kimberley 2018; Wu 2020), and three were at high risk of bias (Chang 2021; Wang 2024; Li 2022).

Regarding the risk of bias for quality of life (assessed with the SIS), we assessed this in three studies (Dawson 2021; Kimberley 2018; Li 2022). Two studies had some concerns (Dawson 2021; Kimberley 2018), and one study was at high risk of bias (Li 2022).

We have presented the support for the risk of bias judgements in Supplementary material 18.

Synthesis of results

See Summary of findings 1, Supplementary material 6, and Supplementary material 7.

All studies contributed data to these comparisons, although not for all the outcomes. While several trial authors agreed to share data for the meta-analyses (Dawson 2016; Dawson 2021; Kimberley 2018; Chang 2021), when the review was submitted for editorial approval, we obtained unpublished data from only one study (Chang 2021).

VNS interventions plus rehabilitation versus rehabilitation alone

Ten studies compared the effectiveness of VNS in addition to rehabilitation versus rehabilitation alone (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018; Li 2022; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025). All studies evaluated the participants at short-term, three studies assessed at medium-term (Dawson 2021; Kimberley 2018; Li 2022), and one study assessed at long-term (Li 2022).

We have presented the analyses at medium-term and long-term in Supplementary material 20.

1.1. Critical outcome: UE motor function

All ten included studies used the UE-FMA, or its simplified version (Zhang 2025), to assess UE motor function. Zhang 2023 reported two different interventions involving VNS coupled with rehabilitation.

We observed heterogeneity in the forest plot (Analysis 1.1), which prompted further investigation. We identified one comparison, Zhang 2023, in which the content and dose of the add-on therapies differed substantially between the intervention and control groups. Thus, we excluded this comparison from the pooled analysis.

The evidence is very uncertain about the effect of VNS coupled with rehabilitation on UE motor function compared to rehabilitation alone (SMD 1.22, 95% CI 0.68 to 1.77, 95% prediction interval (PI) −0.25 to 2.70; 10 studies, 499 participants; very-low certainty evidence; Figure 2; Analysis 1.2). The re-expressed MD (MD 8.03, 95% CI 4.48 to 11.66) exceeds the threshold of the MID (6.6 points).

Sensitivity analyses for comparison 1.1

We excluded six studies at high risk of bias (Capone 2017; Chang 2021; Wang 2024; Li 2022; Zhang 2023; Zhang 2025), which left four studies (Dawson 2016; Dawson 2021; Kimberley 2018; Wu 2020). The pooled estimate (SMD 1.05, 95% CI −0.08 to 2.19) overlaps our main analysis result.

After we excluded four studies with imputed data (Kimberley 2018; Li 2022; Zhang 2023; Zhang 2025), we had six studies left(Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Wang 2024; Wu 2020). The pooled estimate showed a similar effect (SMD 0.99, 95% CI 0.21 to 1.77, 95% PI −0.63 to 2.61).

Inclusion of one outlying study, Zhang 2023, resulted in a total of 11 studies (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018; Li 2022; Wang 2024; Wu 2020; Zhang 2023; Zhang 2025). The pooled estimate showed a similar effect (SMD 0.72, 95% CI 0.08 to 1.75, 95% PI −1.57 to 3.41).

1.1.1. Subgroup analyses: stroke phase

We compared studies whose findings were collected in the (hyper-)acute and early subacute phases with those collected in the late subacute and chronic phases. We identified a difference between subgroups (Chi2 = 11.81, df = 1, P = 0.0006; Analysis 2.1), suggesting a larger magnitude of effect in studies conducted in the (hyper-)acute and early subacute phases (SMD 2.11, 95% CI 0.69 to 3.53) compared with those conducted in the late subacute and chronic phases (SMD 0.84, 95% CI 0.44 to 1.25).

1.1.2. Subgroup analyses: invasive versus non-invasive VNS

We compared studies involving invasive VNS with studies involving non-invasive VNS. We identified a difference between subgroups (Chi2 = 4.89, df = 1, P =0.03; Analysis 2.2), indicating that there may be a larger magnitude of effect in studies involving non-invasive VNS (SMD 1.42, 95% CI 0.63 to 2.21) compared to those involving invasive VNS (SMD 0.69, 95% CI 0.35 to 1.02).

1.1.3. Subgroup analyses: impairment severity

We compared studies involving participants with severe motor impairments to studies involving participants with moderate to mild motor impairments. The test for subgroup difference did not indicate a difference between subgroups (Chi2 = 0.02, df = 1, P = 0.89; Analysis 2.3).

1.2. Critical outcome: SAEs

Nine studies reported SAEs (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018; Li 2022; Wang 2024; Wu 2020; Zhang 2025). Three studies did not distinguish between SAEs occurring between short-term and medium-term time points (Dawson 2016; Dawson 2021; Kimberley 2018).

End of treatment

Eight studies reported the number of participants who suffered SAEs in experimental and control intervention (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Li 2022; Wang 2024; Wu 2020; Zhang 2025). Kimberley 2018 only reported the total number of SAEs (not per group).

The evidence suggests that VNS results in little to no increased risk of SAEs (RR 2.38, 95% CI 0.77 to 7.30; 8 studies, 416 participants; low-certainty evidence; Figure 3).

Sensitivity analyses for comparison 1.2

We excluded five studies at high risk of bias (Capone 2017; Chang 2021; Li 2022; Wang 2024; Zhang 2025), which left three studies (Dawson 2016; Dawson 2021; Wu 2020). When pooled together, these studies showed a similar effect (RR 2.12, 95% CI 0.68 to 6.61).

We conducted two sensitivity analyses using the Mantel-Haenszel exact method (RR 2.38, 95% CI 0.77 to 7.30), and an inverse variance model with Restricted Maximum Likelihood estimator (RR 2.2, 95% 0.75 to 6.49). The differences were minor.

1.3. Important outcome: UE activity

Six studies evaluated the effect of VNS on UE activity using either the ARAT (Dawson 2016; Wang 2024), or the Wolf Motor Function Test (Chang 2021; Kimberley 2018; Li 2022; Wu 2020).

The evidence is very uncertain about the effect of VNS coupled with rehabilitation on UE activity (SMD 0.88, 95% CI −0.09 to 1.86, 95% PI −1.52 to 3.29; 6 studies, 186 participants; very-low certainty evidence; Figure 4; Analysis 1.5).

Sensitivity analyses for comparison 1.3

We excluded three studies at high risk of bias (Chang 2021; Wang 2024; Li 2022), which left three studies (Dawson 2016; Kimberley 2018; Wu 2020). The pooled estimate (SMD 0.86, 95% CI –1.71 to 3.43) showed similar results.

We excluded two studies with imputed data (Kimberley 2018; Li 2022), which left four studies. The pooled estimate (SMD 0.92, 95% CI –0.74 to 2.58) showed similar results.

1.4. Important outcome: quality of life

Four studies evaluated the effect of VNS on quality of life (Dawson 2016; Dawson 2021; Kimberley 2018; Li 2022). However, data were available from only three studies (Dawson 2021; Kimberley 2018; Li 2022), and used the SIS or its hand function subdomain.

The evidence is very uncertain about the effect of VNS coupled with rehabilitation on quality of life (SMD 0.04, 95% CI –0.30 to 0.37; 3 studies, 180 participants; very-low certainty evidence; Figure 5; Analysis 1.8).

Other outcomes

We have presented the synthesis for other outcomes in Supplementary material 19.

Equity assessment

We compared VNS studies conducted in middle-income countries versus high-income countries using subgroup analysis. There was a subgroup difference in favour of studies conducted in middle- income countries (Chi2 = 13.52; df = 1; P < 0.001; Analysis 2.4).

The effect of VNS on post-stroke UE motor function was larger in studies in middle-income countries (SMD 1.74, 95% CI 0.95 to 2.54) compared to that in high-income countries (SMD 0.60, 95% CI 0.27 to 0.93).

Due to insufficient data, it was not feasible to explore differences between sex groups (women versus men).

Reporting biases

All but three included VNS studies published their protocol on a clinical trials register (Wang 2024; Zhang 2023; Zhang 2025). Of these, six were registered prospectively (Capone 2017; Chang 2021; Dawson 2016; Dawson 2021; Kimberley 2018; Wu 2020), and one retrospectively (Li 2022). Differences between trials' published protocol and publications are presented in Table 2.

The number of studies was small and visual inspection of the funnel plot did not suggest a clear symmetric or asymmetric distribution around the pooled effect estimate (Analysis 1.2; Figure 6).

DISCUSSION

Summary of main results

In this Cochrane review, we included 10 RCTs with a total of 547 participants. All studies were published within the past 10 years, highlighting the growing interest in VNS for UE stroke rehabilitation in recent years. Three studies combined rehabilitation with invasive VNS, and seven studies combined rehabilitation with non-invasive VNS.

Ten studies compared the effect of VNS in addition to rehabilitation with rehabilitation alone on 'UE motor function' and reported 'SAEs' at short-term. All studies assessed UE motor function using the UE-FMA or its simplified version. Based on very-low certainty evidence, we are uncertain about the effect of VNS on UE motor function compared to rehabilitation alone. Based on low-certainty evidence, VNS may result in little to no increased risk of SAEs compared to rehabilitation alone.

For the short-term outcomes of 'UE activity', and 'quality of life', we assessed the certainty of the evidence as very low. Thus, we are very uncertain about the effect of VNS on UE activity (as measured with the ARAT or the Wolf Motor Function Test) and on quality of life (as measured with the SIS or its hand function subdomain) compared to rehabilitation alone.

Limitations of the evidence included in the review

The completeness of the evidence is limited by several factors. Firstly, we only included 10 studies with low to moderate sample sizes, which primarily assessed impairment-based outcomes (such as the FMA-UE) with limited attention to other outcomes, such as LE motor function, manual dexterity, and at medium and long-term. Secondly, the exclusion (from some studies) of adults over 80 years of age, individuals with cognitive impairments, and those with comorbidities restricts generalisability. Most studies also focused on ischaemic stroke, leaving gaps for haemorrhagic stroke. Moreover, sex-specific data were insufficient across studies, limiting the ability to explore potential differences in VNS effects between females and males. Thirdly, the heterogeneity in intervention protocols, differing in VNS delivery (invasive versus non-invasive), stimulation parameters, and add-on session modalities (RAT, UE training, or postural training), further complicates interpretation. Lastly, while safety data were generally reassuring, reporting was inconsistent. Rare SAEs, such as vocal cord palsy, highlight the need for rigorous monitoring in future trials. To improve the body of evidence, future research should include more diverse stroke populations and incorporate other patient-centred outcomes with long-term follow-up.

Using the GRADE approach, we found the certainty of evidence to be low to very low, indicating an important level of uncertainty across outcomes. Imprecision was important as included studies had limited sample sizes and wide CIs. Considerable statistical heterogeneity was often observed, likely influenced by variations in stimulation type and add-on therapy content.

The overall risk of bias was unclear to high. Most studies had an overall high risk of bias due to unclear randomisation, deviations from intended interventions, and selective reporting of results. In addition, we noticed a risk of publication bias as several completed studies have not published their results. This further limits confidence in the findings.

In terms of applicability, re-expression of the mean VNS effect on UE motor function on the UE-FMA scale showed an effect size that exceeds the threshold of clinical relevance. However, certainty of evidence is very low, which limits its clinical impact. Similarly, while subgroup analyses exploring stroke phase and VNS type suggested potentially larger effects in (hyper-)acute/early subacute phases

and for non-invasive VNS, the evidence for these subgroup effects remains very uncertain. Owing to the very low-certainty evidence and their exploratory nature, they should be interpreted with caution.

Limitations of the review processes

Despite comprehensive searches across multiple databases, trial registries, and hand searching, it is possible that we may have missed some studies. Only 10 studies met the inclusion criteria, and we excluded many studies due to methodological or relevance issues. Restricting the review to RCTs led to the exclusion of observational studies and pilot trials, which may have limited the comprehensiveness of this work.

As interventions varied (invasive and non-invasive VNS with add- on therapies, such as UE functional training, RAT, or postural rehabilitation), there may be a potential bias regarding how we categorised and pooled the studies. Moreover, the limited number of included studies meant we were unable to undertake subgroup and sensitivity analyses for all outcomes.

Agreements and disagreements with other studies or reviews

Currently, there are at least 11 systematic reviews that have assessed the effect of VNS on post-stroke UE motor function [50, 51, 52, 54, 55, 56, 157, 158, 159, 160, 161]. Most also investigated other outcomes, such as UE activity [50, 52, 54, 55, 56, 158, 159, 160, 161], quality of life [50, 54, 157], functional independence [52, 161], and safety [50, 51, 52, 54, 55, 56, 157, 158, 159, 160].

While published systematic reviews suggest that VNS may lead to improvements in UE motor function and activity [50, 51, 52, 54, 55, 56, 157, 158, 159, 160, 161], in this Cochrane review the pooled estimates were imprecise and did not support firm conclusions. Evidence regarding quality of life and SAEs was also uncertain, generally aligning with other systematic reviews that reported no clear effect of VNS on quality of life and no evidence of an increased or decreased risk of SAEs [50, 51, 52, 54, 55, 56, 157, 158, 159, 160].

Finally, this Cochrane review highlights gaps that are consistent with other systematic reviews [50, 51, 52, 54, 55, 56, 157, 158, 159, 160, 161], such as the lack of long-term follow-up and patient- centred outcomes. While some studies incorporated quality-of-life measures, results were inconsistently reported, limiting the ability to assess the holistic impact of VNS. Addressing these gaps through future research will be essential to provide a more comprehensive understanding of VNS interventions in stroke rehabilitation. More research is necessary to reach a high level of evidence and better understand the most effective approach to combining VNS with stroke rehabilitation.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence on the benefits and harms of vagus nerve stimulation (VNS) on upper extremity (UE) motor function, serious adverse events, UE activity, and quality of life is limited. Thus, for all outcomes examined in this Cochrane review, we are uncertain whether VNS is effective and safe to use. Current evidence is limited due to the small number of randomised controlled trials (RCTs) available and their relatively small sample sizes. Substantial heterogeneity in study designs, patient characteristics, and intervention protocols further limits the applicability of the current findings to clinical practice. Evidence for longer-term follow-up is sparse.

Equity-related implications for practice

There is currently insufficient evidence to support any equity- related considerations in clinical practice. Although one subgroup analysis suggested a greater effect on UE motor function in studies conducted in middle-income countries, this finding is highly uncertain due to the small number of included studies and their higher risk of bias. In addition, insufficient data were available to assess whether effects differed by biological sex (male/female).

Implications for research

Future research should prioritise large, high-quality RCTs. Consistency in VNS and add-on protocols, outcome measures, and reporting standards is essential to reduce heterogeneity and improve the comparability of results. Future studies should also ensure adequate sample sizes to detect clinically meaningful differences and include long-term follow-up to assess the durability of treatment effects. Furthermore, efforts should be made to publish all trial outcomes to minimise publication bias and provide a clearer picture of the true benefits and risks of VNS interventions.

Equity-related implications for research

Larger, adequately powered RCTs and harmonised reporting of participant characteristics would enable meaningful subgroup analyses to assess whether the benefits and harms of VNS interventions differ across population groups. In particular, future studies should ensure balanced representation and transparent reporting of biological sex (male/female), as the current evidence base does not allow sex-disaggregated analyses. Improved reporting of socioeconomic and contextual factors would further support robust evaluation of equity-related effects.

SUPPLEMENTARY MATERIALS

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Analyses

Supplementary material 7 Data package

Supplementary material 8 Deviations from protocol

Supplementary material 9 Information extracted using the data collection form

Supplementary material 10 Risk of bias: domains covered and methods for cross-over and cluster-RCTs

Supplementary material 11 Methods for re-expressing SMDs as MDs

Supplementary material 12 The splitting approach

Supplementary material 13 Unit of analyses issues: methods for three-arm studies and cluster-RCTs

Supplementary material 14 Management of outlying studies in case of heterogeneity

Supplementary material 15 Methods for calculating confidence and prediction intervals

Supplementary material 16 Application of the GRADE approach and prespecified rules

Supplementary material 17 Included studies' participants' information

Supplementary material 18 Support for judgements regarding the assessment of risk of bias in included studies

Supplementary material 19 Other outcomes for Comparison 1. VNS plus rehabilitation versus rehabilitation alone

Supplementary material 20 Medium and long-term outcomes for Comparison 1. VNS plus rehabilitation versus rehabilitation alone

ADDITIONAL INFORMATION

Disclosure of artificial intelligence use

We used ChatGPT 5.2. to assist with language editing and stylistic refinement. The authors take full responsibility for the content of the review.

Contributions of authors

Gauthier Everard was involved in conceptualisation, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualisation, and writing the original review draft.

Ita Daryanti Saragih was involved in conceptualisation, data curation, formal analysis, investigation, methodology, software, validation, and writing and editing the review.

Jesse Dawson was involved in conceptualisation, and writing and editing the review.

Dame Elysabeth Tarihoran was involved in conceptualisation, and writing and editing the review.

Shailesh M Advani was involved in conceptualisation, and writing and editing the review.

Huey-Ming Tzeng was involved in conceptualisation, and writing and editing the review.

Bih-O Lee was involved in conceptualisation, and writing and editing the review.

Geertruida E Bekkering was involved in conceptualisation, investigation, methodology, project administration, resources, supervision, validation, and writing and editing the review.

Declarations of interest

Gauthier Everard: none known.

Ita Daryanti Saragih: none known.

Jesse Dawson: works as a stroke consultant, and received funding from MicroTransponder Inc since January 2012 for costs of enrolment for clinical trials and travel expenses. He is an investigator of several RCTs included in this review [49, 60, 61], and therefore was not involved in the selection of studies, data extraction and management, risk of bias assessments, and certainty of the evidence assessments. No other relevant conflict of interest.

Dame Elysabeth Tarihoran: none known.

Shailesh Advani: none known.

Huey-Ming Tzeng: registered nurse (by training) at the University of Texas Medical Branch (Galveston, TX, USA) but does provide direct patient care.

Bih-O Lee: works as health professional in Kaohsiung Medical University (Taiwan).

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Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library: full search strategies for each database (Supplementary material 1); full citations of each unique report for all studies included (Supplementary material 2), excluded (Supplementary material 3), awaiting classification (Supplementary material 4), and ongoing (Supplementary material 5); study data, including study information, study arms, and study results or test data (Supplementary material 7); consensus risk of bias assessments (Supplementary material 18); and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows (Supplementary material 6). Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods [96]. We used a script from Efthimiou 2018 in R to generate analyses outside RevMan [108, 109]. Template data extraction forms from Excel are available from the review authors on reasonable request.

REFERENCES

1. Copenhagen Trial Unit's Trial Sequential Analysis Software (TSA Software). Version 0.9.5.10 Beta. Copenhagen Trial Unit, 2017. Available at ctu.dk/tsa.

2. Hankey GJ. Stroke. Lancet 2017;389(10069):641-54.

3. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(7):2064-89.

4. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. Neurology 2021;20(10):795-820. [DOI: 10.1016/S1474-4422(21)00252-0]

5. Gorelick PB. The global burden of stroke: persistent and disabling. Lancet. Neurology 2019;18(5):417-8.

6. Fekadu G, Chelkeba L, Kebede A. Risk factors, clinical presentations and predictors of stroke among adult patients admitted to stroke unit of Jimma University Medical Center, South West Ethiopia: prospective observational study. BMC Neurology 2019;19(1):187.

7. Gil-Salcedo A, Dugravot A, Fayosse A, Landré B, Jacob L, Bloomberg M, et al. Pre-stroke disability and long-term functional limitations in stroke survivors: findings from more of 12 years of follow-up across three international surveys of aging. Frontiers in Neurology 2022;13:888119.

8. Mead GE, Sposato LA, Sampaio Silva G, Yperzeele L, Wu S, Kutlubaev M, et al. A systematic review and synthesis of global stroke guidelines on behalf of the World Stroke Organization. International Journal of Stroke 2023;18(5):499-531.

9. Prabhakaran S, Gonzalez NR, Zachrison KS, Adeoye O, Alexandrov AW, Ansari SA, et al. 2026 guideline for the early management of patients with acute ischemic stroke: a guideline from the American Heart Association/American Stroke Association. Stroke 2026 Jan 26 [Epub ahead of print]. [DOI: 10.1161/STR.0000000000000513]

10. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, Jong A, et al. Canadian Stroke Best Practice recommendations: rehabilitation, recovery, and community participation following stroke. Part one: rehabilitation and recovery following stroke; 6th edition update 2019. International Journal of Stroke 2020;15(7):763-88.

11. Alt Murphy M, Munoz-Novoa M, Heremans C, Branscheidt M, Cabanas-Valdés R, Engelter ST, et al. European Stroke Organisation (ESO) guideline on motor rehabilitation. European Stroke Journal 2025;10(4):1160-88.

12. Lee KB, Lim SH, Kim KH, Kim KJ, Kim YR, Chang WN, et al. Six-month functional recovery of stroke patients: a multi- time-point study. International Journal of Rehabilitation Research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation 2015;38(2):173-80.

13. Su F, Xu W. Enhancing brain plasticity to promote stroke recovery. Frontiers in Neurology 2020;11:554089.

14. Stinear C. Prediction of recovery of motor function after stroke. Lancet. Neurology 2010;9(12):1228-32.

15. Howland RH. Vagus nerve stimulation. Current Behavioral Neuroscience Reports 2014;1(2):64-73.

16. Afra P, Adamolekun B, Aydemir S, Watson GD. Evolution of the vagus nerve stimulation (VNS) therapy system technology for drug-resistant epilepsy. Frontiers in Medical Technology 2021;3:696543.

17. Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy & Behavior 2018;88S:2-10.

18. Arsava EM, Topcuoglu MA, Ay I, Ozdemir AO, Gungor IL, Togay Isikay C, et al. Assessment of safety and feasibility of non- invasive vagus nerve stimulation for treatment of acute stroke. Brain Stimulation 2022;15(6):1467-74.

19. Li JN, Xie CC, Li CQ, Zhang GF, Tang H, Jin CN, et al. Efficacy and safety of transcutaneous auricular vagus nerve stimulation combined with conventional rehabilitation training in acute stroke patients: a randomized controlled trial conducted for 1 year involving 60 patients. Neural Regeneration Research 2022;17(8):1809-13.

20. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, et al. Safety and tolerability of transcutaneous vagus nerve stimulation in humans: a systematic review. Brain Stimulation 2018;11(6):1225-38.

21. Malakouti N, Serruya MD, Cramer SC, Kimberley TJ, Rosenwasser RH. Making sense of vagus nerve stimulationfor stroke. Stroke 2024;55:519-22.

22. Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. Journal of Anatomy 2020;236(4):588-611.

23. Zhu S, Zhang X, Zhou M, Kendrick KM, Zhao W. Therapeutic applications of transcutaneous auricular vagus nerve stimulation with potential for application in neurodevelopmental or other pediatric disorders. Frontiers in Endocrinology 2022;13:1000758.

24. Gadeyne S, Mertens A, Carrette E, Van den Bossche F, Boon P, Raedt R, et al. Transcutaneous auricular vagus nerve stimulation cannot modulate the P3b event-related potential in healthy volunteers. Clinical Neurophysiology 2022;135:22-9.

25. Giraudier M, Ventura-Bort C, Burger AM, Claes N, D'Agostini M, Fischer R. Evidence for a modulating effect of transcutaneous auricular vagus nerve stimulation (taVNS) on salivary alpha-amylase as indirect noradrenergic marker: a pooled mega-analysis. Brain Stimulation 2022;15(6):1378-88.

26. Sharon O, Fahoum F, Nir Y. Transcutaneous vagus nerve stimulation in humans induces pupil dilation and attenuates alpha oscillations. Journal of Neuroscience 2021;41(2):320-30.

27. Engineer ND, Kimberley TJ, Prudente CN, Dawson J, Tarver WB, Hays SA. Targeted vagus nerve stimulation for rehabilitation after stroke. Frontiers in Neuroscience 2019;13:280.

28. Krakauer JW. Functional imaging of motor recovery after stroke: remaining challenges. Current Neurology and Neuroscience Reports 2004;4(1):42-6.

29. Nudo RJ. Mechanisms for recovery of motor function following cortical damage. Current Opinion in Neurobiology 2006;16(6):638-44.

30. Olsen LK, Solis JE, McIntire LK, Hatcher-Solis CN. Vagus nerve stimulation: mechanisms and factors involved in memory enhancement. Frontiers in Human Neuroscience 2023;17:1152064.

31. Shen H, Fuchino Y, Miyamoto D, Nomura H, Matsuki N. Vagus nerve stimulation enhances perforant path-CA3 synaptic transmission via the activation of β-adrenergic receptors and the locus coeruleus. International Journal of Neuropsychopharmacology 2012;15(4):523-30.

32. Olsen LK, Moore RJ, Bechmann NA, Ethridge VT, Gargas NM, Cunningham SD, et al. Vagus nerve stimulation-induced cognitive enhancement: hippocampal neuroplasticity in healthy male rats. Brain Stimulation 2022;15(5):1101-10.

33. Furmaga H, Carreno FR, Frazer A. Vagal nerve stimulation rapidly activates brain-derived neurotrophic factor receptor TrkB in rat brain. PLOS One 2012;7(5):e34844. [DOI: 10.1371/journal.pone.0034844]

34. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience 2002;111(4):815-35.

35. Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. Journal of Psychiatry Neuroscience 2009;34(4):272-80.

36. Ma J, Qiao P, Li Q, Wang Y, Zhang L, Yan LJ, et al. Vagus nerve stimulation as a promising adjunctive treatment for ischemic stroke. Neurochemistry International 2019;131:104539.

37. Kandel ER, Dudai Y, Mayford MR. The molecular and systems biology of memory. Cell 2014;157(1):163-86.

38. Ay I, Lu J, Ay H, Gregory Sorensen A. Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia. Neuroscience Letters 2009;459(3):147-51.

39. Biggio F, Gorini G, Utzeri C, Olla P, Marrosu F, Mocchetti I, et al. Chronic vagus nerve stimulation induces neuronal plasticity in the rat hippocampus. International Journal of Neuropsychopharmacology 2009;12(9):1209-21.

40. Meyers EC, Solorzano BR, James J, Ganzer PD, Lai ES, Rennaker RL, et al. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. Stroke 2018;49(3):710-7.

41. Cheng K, Wang Z, Bai J, Xiong J, Chen J, Ni J. Research advances in the application of vagus nerve electrical stimulation in ischemic stroke. Frontiers in Neuroscience 2022;16:1043446.

42. Lindemann J, Rakers C, Matuskova H, Simon BJ, Kinfe T, Petzold GC. Vagus nerve stimulation reduces spreading depolarization burden and cortical infarct volume in a rat model of stroke. PLOS One 2020;15(7):e0236444.

43. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nature Medicine 2011;17(4):439-47.

44. Hartings JA, Shuttleworth CW, Kirov SA, Ayata C, Hinzman JM, Foreman B, et al. The continuum of spreading depolarizations in acute cortical lesion development: examining Leao's legacy. Journal of Cerebral Blood Flow and Metabolism 2017;37(5):1571-94.

45. Nakamura H, Strong AJ, Dohmen C, Sakowitz OW, Vollmar S, Sue M, et al. Spreading depolarizations cycle around and enlarge focal ischaemic brain lesions. Brain: Broad Research in Artificial Intelligence and Neuroscience 2010;133(7):1994-2006.

46. Khodaparast N, Kilgard MP, Casavant R, Ruiz A, Qureshi I, Ganzer PD, et al. Vagus nerve stimulation during rehabilitative training improves forelimb recovery after chronic ischemic stroke in rats. Neurorehabilitation and Neural Repair 2016;30(7):676-84.

47. Donnellan C, Hickey A, Hevey D, O'Neill D. Effect of mood symptoms on recovery one year after stroke. International Journal of Geriatric Psychiatry 2010;25(12):1288-95.

48. Tseng CT, Brougher J, Gaulding SJ, Hassan BS, Thorn CA. Vagus nerve stimulation promotes cortical reorganization and reduces task-dependent calorie intake in male and female rats. Brain Research 2020;1748:147099.

49. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS- REHAB): a randomised, blinded, pivotal, device trial. Lancet 2021;397(10284):1545-53.

50. Liu Y, Zhang L, Zhang X, Ma J, Jia G. Effect of combined vagus nerve stimulation on recovery of upper extremity function in patients with stroke: a systematic review and meta-analysis. Journal of Stroke and Cerebrovascular Diseases 2022;31(6):106390.

51. Ramos-Castaneda JA, Barreto-Cortes CF, Losada- Floriano D, Sanabria-Barrera SM, Silva-Sieger FA, Garcia RG. Efficacy and safety of vagus nerve stimulation on upper limb motor recovery after stroke. A systematic review and meta- analysis. Frontiers in Neurology 2022;13:889953.

52. Xie YL, Wang S, Wu Q, Chen X. Vagus nerve stimulation for upper limb motor impairment after ischemic stroke: a meta-analysis. Medicine 2021;100(46):e27871.

53. Zhang C, Wang JX, Sun FH, Xie YJ, Ou X, Yang SB. The effect of VNS on the rehabilitation of stroke: a meta-analysis of randomized controlled studies. Journal of Clinical Neuroscience 2020;81:421-5.

54. Zhao K, Yang J, Huang J, Zhao Z, Qu Y. Effect of vagus nerve stimulation paired with rehabilitation for upper limb function improvement after stroke: a systematic review and meta-analysis of randomized controlled trials. International Journal of Rehabilitation Research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation 2021;45(2):99-108.

55. Abdullahi A, Wong TW, Ng SS. Effects and safety of vagus nerve stimulation on upper limb function in patients with stroke: a systematic review and meta-analysis. Scientific Reports 2023;13(1):15415.

56. Wei T, Ge X, Lu L, Li J, Xu P, Wu Q. Efficacy and safety of vagus nerve stimulation on upper extremity motor function in patients with stroke: a meta-analysis of randomized controlled trials. NeuroRehabilitation 2023;53(3):253-67. [DOI: 10.3233/NRE-230106]

57. Zhang J, Xing Y, Du W, Liu L, Di X. Analysis of the effect of combined rehabilitation training and transcutaneous vagus nerve electrical stimulation on promoting central nervous system remodeling in stroke patients. Brain Research 2025;1851:149460.

58. Zhang X, Liu Y, Jin Z. Effect of transcutaneous auricular vagus nerve stimulation combined with bilateral arm training on upper limbmotor function of stroke patients. Chinese Journal of Rehabilitation Theory and Practice 2023;29(3):280-5.

59. Wang MH, Wang YX, Xie M, Chen LY, He MF, Lin F, et al. Transcutaneous auricular vagus nerve stimulation with task- oriented training improves upper extremity function in patients with subacute stroke: a randomized clinical trial. Frontiers in Neuroscience 2024;18:1346634.

60. Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Tarver B, et al. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. Stroke 2016;47(1):143-50.

61. Kimberley TJ, Pierce D, Prudente CN, Francisco GE, Yozbatiran N, Smith P, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke. Stroke 2018;49(11):2789-92.

62. Capone F, Miccinilli S, Pellegrino G, Zollo L, Simonetti D, Bressi F, et al. Transcutaneous vagus nerve stimulation combined with robotic rehabilitation improves upper limb function after stroke. Neural Plasticity 2017;2017:876507.

63. Wu D, Ma J, Zhang L, Wang S, Tan B, Jia G. Effect and safety of transcutaneous auricular vagus nerve stimulation on recovery of upper limb motor function in subacute ischemic stroke patients: a randomized pilot study. Neural Plasticity 2020;2020:8841752.

64. Chang JL, Coggins AN, Saul M, Paget-Blanc A, Straka M, Wright J, et al. Transcutaneous Auricular Vagus Nerve Stimulation (tAVNS) delivered during upper limb interactive robotic training demonstrates novel antagonist control for reaching movements following stroke. Frontiers in Neuroscience 2021;15:767302.

65. Kwakkel G, Dobkin BH. Vagus nerve stimulation for upper limb function: significant difference, but clinically important? Stroke 2021;52(10):3407-9.

66. Higgins JP, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. Version August 2023. Cochrane, London. https://www.cochrane.org/authors/handbooks-and-manuals/mecir-manual.

67. 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;372:71.

68. Everard G, Saragih ID, Dawson J, Tarihoran DE, Advani SM, Tzeng HM, et al. Vagus nerve stimulation to improve post- stroke motor function and activity. Cochrane Database of Systematic Reviews 2024, Issue 2. Art. No: CD015859. [DOI:10.1002/14651858.CD015859]

69. McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV, Thomas J. Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

70. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the Stroke Recovery and Rehabilitation Roundtable Taskforce. International Journal of Stroke 2017;12(5):444-50.

71. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation Medicine 1975;7(1):13-31. [PMID: 1135616]

72. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. CMAJ: Canadian Medical Association Journal 2008;178(9):1181-4.

73. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. International Journal of Stroke 2017;12(5):451-61.

74. Lanctôt KL, Lindsay MP, Smith EE, Sahlas DJ, Foley N, Gubitz G, et al. Canadian Stroke Best Practice recommendations: mood, cognition and fatigue following stroke; update 2019. International Journal of Stroke 2020;15(6):668-88.

75. Pohl J, Held JP, Verheyden G, Alt Murphy M, Engelter S, Flöel A, et al. Consensus-based core set of outcome measures for clinical motor rehabilitation after stroke - a Delphi study. Frontiers in Neurology 2020;11:875.

76. Prange-Lasonder GB, Alt Murphy M, Lamers I, Hughes AM, Buurke JH, Feys P, et al. European evidence-based recommendations for clinical assessment of upper limb in neurorehabilitation (CAULIN): data synthesis from systematic reviews, clinical practice guidelines and expert consensus. Journal of Neuroengineering and Rehabilitation 2021;18(1):162.

77. Van Criekinge T, Heremans C, Burridge J, Deutsch JE, Hammerbeck U, Hollands K, et al. Standardized measurement of balance and mobility post-stroke: consensus-based core recommendations from the third Stroke Recovery and Rehabilitation Roundtable. Neurorehabilitation and Neural Repair 2023;19(2):158-68.

78. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47(6):e98-169.

79. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the Action Research Arm test. Neurorehabilitation and Neural Repair 2008;22(1):78-90.

80. Lin KC, Hsieh YW, Wu CY, Chen CL, Jang Y, Liu JS. Minimal detectable change and clinically important difference of the Wolf Motor Function Test in stroke patients. Neurorehabilitation and Neural Repair 2009;23(5):429-34.

81. Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing Wolf Motor Function test as outcome measure for research in patients after stroke. Stroke 2001;32(7):1635-9.

82. Gregson JM, Leathley M, Moore AP, Sharma AK, Smith TL, Watkins CL. Reliability of the Tone Assessment Scale and the modified Ashworth scale as clinical tools for assessing poststroke spasticity. Archives of Physical Medicine and Rehabilitation 1999;80(9):1013-6.

83. Morris S. Ashworth and Tardieu scales: their clinical relevance for measuring spasticity in adult and paediatric neurological populations. Physical Therapy Reviews 2002;7(1):53-62.

84. Brunnstrom S. Motor testing procedures in hemiplegia: based on sequential recovery stages. Physical Therapy 1966;46(4):357-75.

85. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block test of manual dexterity. American Journal of Occupational Therapy 1985;39(6):386-91.

86. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the Nine-Hole Peg test of finger dexterity. Occupational Therapy Journal of Research 1985;5(1):24-38.

87. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The Stroke Impact Scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke 1999;30(10):2131-40.

88. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine 2001;33(5):337-43.

89. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 1983;67(6):361-70.

90. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of Internal Medicine 2006;166(10):1092-7.

91. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.

92. Dávalos A, Blanco M, Pedraza S, Leira R, Castellanos M, Pumar JM, et al. The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction. Neurology 2004;62(12):2187-92.

93. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler

J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available fromtraining.cochrane.org/handbook.

94. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 14 November 2023. Available at covidence.org.

95. Li T, Higgins JP, Deeks JJ, editor(s). Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

96. Review Manager (RevMan). Version 10.0.0. The Cochrane Collaboration, 2026. Available at revman.cochrane.org.

97. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

98. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

99. Higgins JP, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

100. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc, 1988.

101. Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T,

Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook.

102. Higgins JP, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

103. Rücker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. Research Synthesis Methods 2017;8(4):392-403.

104. Welch VA, Petkovic J, Jull J, Hartling L, Klassen T, Kristjansson E, et al. Chapter 16: Equity and specific populations. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

105. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014;14(1):135.

106. PlotDigitizer. Version 3.1.6. PORBITAL, 2001. Available from https://plotdigitizer.com/.

107. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34. [PMID: 9310563]

108. R: A language and environment for statistical computing. Version 4.3.2. Vienna, Austria: R Foundation for Statistical Computing, 2017. Available at www.R-project.org.

109. Efthimiou O. Practical guide to the meta-analysis of rare events. BMJ Mental Health 2018;21(2):72-6.

110. Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

111. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ 2020;368:l6890.

112. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002;21(11):1539-58.

113. Woytowicz E, Rietschel J, Goodman R, Conroy S, Sorkin J, Whitall J, et al. Determining levels of upper extremity movement impairment by applying a cluster analysis to the Fugl-Meyer Assessment of the upper extremity in chronic stroke. Archives of Physical Medicine and Rehabilitation 2017;98(3):456-62.

114. Hawe P, Shiell A, Riley T. Complex interventions: how "out of control" can a randomised controlled trial be? BMJ 2004;328(7455):1561-3.

115. Pope C, Mays N, Popay J. Synthesising Qualitative and Quantitative Health Evidence: A Guide to Methods. Buckingam (UK): Open University Press, 2007.

116. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

117. GRADEpro GDT. Version accessed 24 November 2023. Hamilton (ON): McMaster University (developed by Evidence Prime), 2023. Available at gradepro.org.

118. Brożek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. Allergy 2009;64(8):1109-16.

119. Capone F, Miccinilli S, Pellegrino G, Zollo L, Simonetti D, Bressi F, et al. Transcutaneous vagus nerve stimulation combined with robotic rehabilitation improves upper limb function after stroke. Neural Plasticity 2017;2017:876507.

120. NCT02878720. Combining non-invasive vagus nerve stimulation and robotic training in upper limb-impaired chronic stroke patients. clinicaltrials.gov/show/NCT02878720 (first received 16 August 2016).

121. Capone F, Miccininilli S, Pellegrino G, Zollo L, Guglielmelli E, Sterzi S, et al. Combining transcutaneous vagus nerve stimulation and upper-limb robotic rehabilitation in chronic stroke patients. Brain Stimulation 2019;12(2):413.

122. Capone F, Miccinilli S, Pellegrino G, Zollo L, Simonetti D, Bressi F, et al. Safety, feasibility, and efficacy of transcutaneous vagus nerve stimulation combined with upper-limb robotic rehabilitation after stroke. Clinical Neurophysiology 2019;130(1):e2.

123. Chang JL, Coggins AN, Saul M, Paget-Blanc A, Straka M, Wright J, et al. Transcutaneous auricular vagus nerve stimulation (tAVNS) delivered during upper limb interactive robotic training demonstrates novel antagonist control for reaching movements following stroke. Frontiers in Neuroscience 2021;15:767302.

124. NCT03592745. Evaluating the use of transcutaneous vagus nerve stimulation (tVNS) and robotic training to improve upper limb motor recovery after stroke [Transcutaneous vagus nerve stimulation (tVNS) and robotic training to improve arm function after stroke]. clinicaltrials.gov/show/NCT03592745 (first received 05 July 2018).

125. Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Tarver B, et al. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. Stroke 2016;47(1):143-50.

126. Dawson J, McLean J, Forbes K, Dixit A, Tarver B, Walters M, et al. Paired vagus nerve stimulation for arm weakness after stroke-analysis of baseline MRI data (10288). Neuromodulation 2016;19(3):e27.

127. Dawson JD, Engineer N, Pierce D, Kimberley T, Tarver B, Dixit A, et al. Vagus nerve stimulation paired with rehabilitation improves upper limb recovery after chronic ischemic stroke. Neuromodulation Technology at the Neural Interface 2015;18(6):e107-399.

128. NCT01669161. A proof-of-concept pilot study assessing vagus nerve stimulation (VNS) paired with rehabilitation for improved upper limb function after stroke (MicroTransponder's Vivistim System)

[Paired vagus nerve stimulation (VNS) with rehabilitation for upper limb function improvement after stroke]. clinicaltrials.gov/show/NCT01669161 (first received 15 August 2015).

129. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS- REHAB): a randomised, blinded, pivotal, device trial. Lancet 2021;397(10284):1545-53.

130. Kimberley TJ, Prudente CN, Engineer ND, Pierce D, Tarver B, Cramer SC, et al. Study protocol for a pivotal randomised study assessing vagus nerve stimulation during rehabilitation for improved upper limb motor function after stroke. European Stroke Journal 2019;4(4):363-77.

131. Liu CY, Russin J, Adelson DP, Jenkins A, Hilmi O, Brown B, et al. Vagus nerve stimulation paired with rehabilitation for stroke: implantation experience from the VNS-REHAB trial. Journal of Clinical Neuroscience 2022;105:122-8.

132. Francisco GE, Kimberley TJ, Engineer N, Prudente C, Tarver WB, Pierce D, et al. Vagus nerve stimulation paired with rehabilitation decreases impairment and improves upper limb function after ischemic stroke: results of a randomized, controlled, multi-center, Phase III trial. 2021 AAPM&R annual assembly abstracts. PM&R 2021;13:S17-8.

133. Turner D, Dawson J, Liu C, Francisco G, Wolf S, O'Dell M, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke: cross-over results from the VNS-REHAB pivotal trial. WSO congress supplement. International Journal of Stroke 2021;16(25):3-170.

134. ISRCTN14280559. Paired vagus nerve stimulation for improved upper limb function after stroke. https://www.isrctn.com/ISRCTN14280559 (first received 14 August 2017).

135. Dawson J, Engineer ND, Cramer SC, Wolf SL, Ali R, O'Dell MW, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor impairment and function after chronic ischemic stroke: subgroup analysis of the randomized, blinded, pivotal, VNS-REHAB device trial. Neurorehabilitation and Neural Repair 2023;37(6):367-73.

136. Dawson J, Liu C, Francisco GE, Cramer SC, Wolf SL, Dixit A, et al. Abstract 1: Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke: sub-group analysis of the randomised, blinded, pivotal, vns-rehab device trial. Abstracts from the American Stroke Association 2022 International Stroke Conference and State-of-the-Science Stroke Nursing Symposium 2022. Stroke 2022;53(Number Suppl 1):no pagination.

137. Kimberley T, Liu C, Francisco G, Wolf S, O'Dell M, Bell K, et al. Effects of VNS paired with rehabilitation for chronic upper limb recovery post stroke: cross-over response. Brain Stimulation 2021;14(6):1715-6.

138. NCT03131960. A pivotal randomized study assessing vagus nerve stimulation (VNS) during rehabilitation for improved upper limb motor function after stroke (VNS-REHAB) [Pivotal study of VNS during rehab after stroke (VNS-REHAB)]. clinicaltrials.gov/show/NCT03131960 (first received 24 April 2017).

139. NCT03945851. Functional MRI and DTI analysis of post VNS therapy rehab changes. clinicaltrials.gov/show/NCT03945851 (first received 29 April 2019).

140. Beovich A, Boose J, Patel R, Wolf SL. Vagus nerve stimulation paired with rehabilitation for chronic stroke: characterizing responders. Journal of Neurologic Physical Therapy 2024;48(4):217-23.

141. Liu CY, Achrol A, Adelson D, Hilmi O, Williams Z, Russin J, et al. Abstract 305: Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischemic stroke. Oral presentations 2022 AANS annual scientific meeting. Journal of Neurosurgery 2022;136:No pagination.

142. Kimberley TJ, Cramer SC, Wolf SL, Liu C, Gochyyev P, Dawson J; VNS-REHAB Trial Group. Long-term outcomes of vagus nerve stimulation paired with upper extremity rehabilitation after stroke. Stroke 2025;56(8):2255-65.

143. Kimberley TJ, Pierce D, Prudente CN, Francisco GE, Yozbatiran N, Smith P, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke. Stroke 2018;49(11):2789-92.

144. Kimberley T, Engineer N, Prudente C, Pierce D, Francisco G, Yozbatiran N, et al. Vagus nerve stimulation paired with rehabilitation for upper limb recovery after stroke: 1-year follow up. Archives of Physical Medicine and Rehabilitation 2019;33(12):1095-6.

145. Francisco GE, Prudente C, Van de Winckel A, Alexander J, Engineer N, Pierce D, et al. Vagus nerve stimulation paired with upper limb rehabilitation after stroke: long-term outcomes. 2020 AAPM&R annual assembly abstracts. PM&R 2020;12:S50

146. Dawson J, Engineer ND, Prudente CN, Pierce D, Francisco G, Yozbatiran N, et al. Vagus nerve stimulation paired with upper-limb rehabilitation after stroke: one-year follow-up. Neurorehabilitation and Neural Repair 2020;34(7):609-15.

147. Francisco GE, Dawson J, Kimberly TJ, Yozbatiran N, Cramer SC, Wolf SL, et al. A randomized double-blind study assessing the effect of vagus nerve stimulation (VNS) during rehabilitation on post-stroke upper limb recovery. WCNR 2018 oral abstracts. Neurorehabilitation and Neural Repair 2018;32(4-5):317-8.

148. Francisco GE, Engineer ND, Dawson J, Kimberley TJ, Cramer SC, Prudente CN, et al. Vagus nerve stimulation paired with upper-limb rehabilitation after stroke: 2- and 3-year follow- up from the pilot study. Archives of Physical Medicine and Rehabilitation 2023;104(8):1180-7.

149. Dawson J, Kimberley TJ, Francisco GE, Smith P, Cramer SC, Wigginton J, et al. Abstracts from the American Heart Association/American Stroke Association 2017 international stroke conference and state-of-the-science stroke sursing symposium. In: Stroke. Vol. 48. 2017:S146.

150. NCT02243020. Study MT-St-02 - stroke - A randomized pilot study assessing vagus nerve stimulation (VNS) during rehabilitation for improved upper limb motor function after stroke (MicroTransponder's Vivistim System) [VNS during rehabilitation for improved upper limb motor function after stroke]. clinicaltrials.gov/show/NCT02243020 (first received 15 September 2014).

151. Li JN, Xie CC, Li CQ, Zhang GF, Tang H, Jin CN, et al. Efficacy and safety of transcutaneous auricular vagus nerve stimulation combined with conventional rehabilitation training in acute stroke patients: a randomized controlled trial conducted for 1 year involving 60 patients. Neural Regeneration Research 2022;17(8):1809-13.

152. ChiCTR1800018962. Transcutaneous auricular vagus nerve stimulation promotes functional recovery after stroke in clinical patients. https://www.chictr.org.cn/showprojEN.html?proj=31434 (first received 19 October 2018).

153. Wu D, Ma J, Zhang L, Wang S, Tan B, Jia G. Effect and safety of transcutaneous auricular vagus nerve stimulation on recovery of upper limb motor function in subacute ischemic stroke patients: a randomized pilot study. Neural Plasticity 2020;2020:8841752.

154. ChiCTR1800019635. Effect of transcutaneous vagus nerve stimulation on the recovery of upper limb motor function in patients with ischemic stroke. https://www.chictr.org.cn/showprojEN.html?proj=32961 (first received 20 November 2018).

155. Zhang L, Yu M, Whang S. Effects of transcutaneous vagus nerve stimulation on the recovery of upper limb motor function in patients with ischemic stroke. Chinese Journal of Rehabilitation Medicine 2020;35(11):1316-20.

156. ACTRN12623000376640. The effect of non invasive auricular vagus nerve stimulation (taVNS) combined with physiotherapy on mobility and balance impairment after stroke [The effect of non invasive auricular vagus nerve stimulation paired with physiotherapy on gait and balance impairments in chronic stroke: a randomised controlled feasibility study]. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12623000376640 (first received 13 April 2023).

157. Ananda R, Roslan MH, Wong LL, Botross NP, Ngim CF, Mariapun J. Efficacy and safety of vagus nerve stimulation in stroke rehabilitation: a systematic review and meta-analysis. Cerebrovascular Diseases (Basel, Switzerland) 2023;52(3):239-50.

158. Wang X, Ding Q, Li T, Li W, Yin J, Li Y, et al. Application of vagus nerve stimulation on the rehabilitation of upper limb dysfunction after stroke: a systematic review and meta- analysis. Frontiers in Neurology 2023;14:1189034. [DOI: 10.3389/fneur.2023.1189034]

159. Gao Y, Zhu Y, Lu X, Wang N, Zhu S, Gong J, et al. Vagus nerve stimulation paired with rehabilitation for motor function, mental health and activities of daily living after stroke: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery and Psychiatry 2023;94(4):257-66.

160. Wei-Jiang, Zhang C, Wang JX, Sun FH, Xie YJ, Ou X, et al. The effect of VNS on the rehabilitation of stroke: a meta- analysis of randomized controlled studies. Journal of Clinical Neuroscience 2020;81:421-5.

161. Yan L, Qian Y, Li H. Transcutaneous vagus nerve stimulation combined with rehabilitation training in the intervention of upper limb movement disorders after stroke: a systematic review. Neuropsychiatric Disease and Treatment 2022;18:2095-106.