Question 53 evidence tables

Question 53: Does vagal nerve stimulation improve outcomes after stroke?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

VNS = vagal nerve stimulation, tVNS = transcutaneous vagal nerve stimulation, a-tDCS = anodal transcranial direct current stimulation, UL = upper limb, FMA-UE = Fugl-Meyer Assessment Upper Extremity Scores, VR = virtual reality, WMFT = Wolf motor function test, FIM = Functional Independence Measurement, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
486	I. Ahmed et al (2022). The Adjunct of Electric Neurostimulation to Rehabilitation Approaches in Upper Limb Stroke Rehabilitation: A Systematic Review With Network Meta-Analysis of Randomized Controlled Trials. Neuromodulation.	Design: SR and network MA – all trials of 'other treatment' +/- VNS or tDCS Subjects: 38 RCTs, 1261 particiants, acute/subacute and chronic stroke, ischaemia/haemorrhage, mild/mod/severe all included	Electric neurostimulation such as tDCS (anodal, cathodal, dual) and VNS (VNS and tVNS) in upper limb stroke rehabilitation. Training = RAT/VR/conventional rehabilitation tDCS sessions = between 5 and 36 sessions at 9-40 mins per session VNS sessions = 10 to 18 sessions at 25-30 mins	FMUE or WMFT as primary outcome measure. Secondary outcomes: Barthel Index or Motor Activity Log Rating Scale and Quality of Movement Scale to measure ADL performance. Network MA used to determine effectiveness	tVNS and a-tDCS improve UL motor function; tVNS and tDCS (a and c) improve ADLs; tVNS seems most effective.	**++** Seems appropriate methodology (don't know about network MA) Comment: However, studies included are extremely heterogeneous There is no rationale for including VNS and tDCS together – likely different mechanisms of action. Even if combining, why not add rTMS
486	I. Ahmed et al (2022). The Adjunct of Electric Neurostimulation to Rehabilitation Approaches in Upper	A systematic Review with Network Meta-Analysis . Included 38 RCTs with 1261 participants with acute/subacute stroke < 6momths or chronic	Intervention examined the effect of Transcranial Direct Current Stimulation , cathodal, anodal or	Primary outcome of upper limb function as measured by FMA-UE & Wolf Motor Function Test(WMFT). Secondary outcomes:	Both tDCS & tVNS showed significant difference in FMA-UE scores in acute/ subacute and chronic patients.	**++** Good quality SR & NMA . However only small number of studies , six in total , for VNS .

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	Limb Stroke Rehabilitation: A Systematic Review With Network Meta-Analysis of Randomized Controlled Trials. Neuromodulation.	stroke >6months . Both ischaemic and haemorrhagic stroke included. Mild, moderate and severe strokes were determined by Fugl-Meyer Assessment Upper Extremity Scores (FMA-UE). Data was extracted independently by 2 reviewers. The Cochrane Risk of Bias assessment tool was used to assess quality.	dual (tDCS) and , Vagus Nerve stimulation , invasive and non invasive (VNS and tVNS) combined with other therapies with one control group with sham tDCS, VNS or tVNS combined with other therapies. Six VNS studies were included . Two studies used non invasive procedure and four, invasive . One study combined VNS with robot assisted training (RAT) and five combined with conventional rehab. Of 32 tDCS studies, six trials used RAT with tDCS and three combined Virtual Reality (VR) with tDCS . VR protocols ranged between intensity of 20 & 30Hz.Number of sessions varied from 10 to 18 and sessions lasted from 25 mins to 60 mins .	Barthel Index or Motor Activity Log Rating Scale and Quality of Movement Scale to measure ADL performance. SUCRA score (numeric ranking score determined by surface under the cumulative ranking curve)was used to rank interventions.	Anodal tDCS versus rehabilitation showed MD:5.23 95%CI [2.45-8.01];P<0.05 Dual Tdcs vs rehabilitation (MD 4.11;95% CI[0.18-8.05] P<0.05 Invasive VNS vs rehab (MD:4.57; 95% CI[0.18-8.05]; P<0.05 tVNS vs rehabilitation: (MD: 5.50;95% CI [0.67-11.67];p<0.05). ADL performance: Cathodal tDCS and Tvns are effective in improving ADL. tVNS versus rehabilitation. (SMD:0.96;95%CI [0.15-2.06];p<0.05) Cathodal tDCSvs rehab (SMD 0.68;95% CI [0.17-1.19]p<0.05 The SUCRA value shows that tVNS is best ranked treatment for improving upper limb motor function. For ADL activities, cathodal Tdcs and tVNSare best ranked treatment with equal SUCRA scores. Both invasive and non-invasive VNS have no impact on adverse events	Methodological and clinical heterogeneity regarding study type , dosage and treatment limits the ability to draw assumptions about modality mechanisms.

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491	Y. L. Xie et al (2021). Vagus nerve stimulation for upper limb motor impairment after ischemic stroke: A meta-analysis. Medicine. 100	Systematic review and meta-analysis of RCTs involving Patients diagnosed with ischemic stroke; 2 indep reviewers. Quality assessed with Cochrane risk of bias ool;	Vagal nerve stimulation (either implanted or cutaneous) PLUS rehabilitation training Control = rehabilitation training alone. 3 trials were of implanted VNS and 3 of surface. Duration of Rx lasted from 15days to 6weeks. The same stimulation settings of 0.8mA, 30Hz frequency, 100ms pulse width with pulse train of 0.5 seconds	Primary outcomes = UL Impairment -Fugl-meyer UL and adverse events. Secondary outcomes = UL function (Wolf motor function test, WMFT) and indep in ADL (Functional Independence Measurement (FIM).	6 trials analysed (234 participants). VNS improved impairment (FM-UL mean diff =3.26, 95%CI 2.79, 3.74, P<.00001) and indep in ADL (FIM mean diff=6.59, 95%CI 5.77, 7.41, P<.00001) but not function (WMFT std mean diff=0.31, 95%CI –0.15, 0.77, P=.19). Adverse events not signifi diff between groups (risk ratio=1.05, 95%CI 0.85, 1.31, P=0.64). Surface SVNS may be more effective than implanted	**++** Good quality SR and MA but small scale – only 6 trials and 234 participants. Sub-group analyses based on very small numbers Conclusion: VNS improved impairment and ADL but not function. and was safe
491	Y. L. Xie et al (2021). Vagus nerve stimulation for upper limb motor impairment after ischemic stroke: A meta-analysis. Medicine. 100	Meta-analysis (N=6, n=234) Patients diagnosed with ischemic stroke; Only RCTs comparing VNS paired with rehabilitation training and with only rehabilitation Training. Participants in all studies were more than 2 weeks post-stroke.	Three studies employed transcutaneous VNS whereas 3 studies adopted implanted VNS as intervention. The stimulation parameters of VNS were different in each study, such as stimulation intensity (mA), frequency (Hz), pulse width (ms), and duration (ms). Three studies employed the same stimulation settings of 0.8mA, 30Hz frequency, 100ms	The primary outcomes were; changes in upper limb function as measured by the Fugl-Meyer Assessment –Upper Limb (FMA-UE), and adverse events related to therapy and devices. The secondary outcomes were; changes in upper limb function as measured by the Wolf Motor Function Test (WMFT) and the Functional Independence Measure (FIM).	Overall the results showed that pairing VNS with rehabilitation training can lead to greater improvements in upper limb function, compared to rehabilitation training only. However there was a difference in outcomes between the studies using implanted VNS (n=3) as an intervention and those studies using transcutaneous VNS (n=3). Transcutaneous VNS produced greater improvements in motor recovery that implanted VNS. Comparisons between groups also showed a greater improvement in motor function in participants	**+** Potential conflicts of interests not declared Excluded studies not listed

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			pulse width with pulse train of 0.5 seconds		receiving VNS and rehabilitation training in the sub-acute phase of stroke, compared to those in the chronic phase (>6 months). There was no differences in safety between the studied groups, indicating VNS is a safe and feasible for patients after ischaemic stroke.	
489	J. N. Li et al (2022). 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. 17: 1809-1813.	Double-blind RCT of 60 acute stroke pts, hospital setting in China. 10.8±7.7, 10.4±6.9 days post stroke	Transcutaneous auricular vagus nerve stimulation (ta-VNS) v sham ta-VNS combined with conventional rehab. 4/52 of 20-min, 5/7 in the hospital The stimulation parameters: 0.3-ms square pulses at 20 Hz for 30 seconds and repeated every 5 minutes. Traditional rehabilitation therapy was used on the limbs and torso, depending on the capacity of the patient. Conventional rehabilitation therapy included postural control, neuromuscular facilitation and	WMFT, FMA (U, L & sensory), SIS, HADS	Couldn't see the actual results- just figures. $p< 0.05$, vs. control group (repeated-measures ANOVA)	- Low quality. Some unclear analysis: The primary functional outcome was the stroke patients' motor and sensory functions at a *given time* after the treatment, as evaluated by WMFT and FMA. sample size was measured to detect a between-group difference of 5 points on the FMA-U with 80% power at a two-tailed significance level of 0.05. Per-protocol analysis, not ITT.

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			sensory integration exercises (Wu et al., 2020).			
489	J. N. Li et al (2022). 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. 17: 1809-1813.	Design - Double-blinded, randomized controlled trial. Setting – Appears to be within an acute hospital but not clearly documented. Subjects – 60 people who have had a stroke within one month were recruited.	An auricular transcutaneous electrical nerve stimulator. 0.3ms square pulses at 20Hz for 30 seconds and repeated every 5 minutes for 20 minutes (mean current intensity 1.7 +/-0.5mA). Delivered five times per week for four weeks. PLACEBO – No current.	Wolf Motor Function Test Fugl-Meyer Assessment Stroke Impact Scale HADS/ OM's taken at baseline, 2 weeks, 1, 3, 6 and 12 months. Primary function outcomes WMFT and FMA	Would be useful to get results directly from the authors. Results are only presented in graphical form. Significant difference between placebo and treatment group from week two in every outcome measure.	**++** Appears to have minimal bias. Difficult to establish actual results as data is only presented in graphical form.
492	K. Zhao et al (2021). 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.	Systematic review and meta-analysis of RCT's. 5 studies included, n=178 Time since stroke: 36.3 +/- 9.23 days (Wu), remainder were all more than 1 year post stroke. Age of participants: ?slightly younger than average Not clear how impaired the study participants were. Intervention programme varied: -6 week course of 2hr therapy sessions, 3x per week -daily for 10 consecutive working days for 1 hour	Invasive VNS or tVNS paired with rehabilitation, 1 study compared with tVNS plus robotic-assisted therapy with sham tVNS with robot assisted therapy (Capone, 2017). Two groups had VNS implanted and control group had sham VNS, 1 group had VNS implanted but control group had rehab only Stimulation parameters for 3	Measured immediately after treatment, no long-term follow-up FMA-UE 5/5 studies Other outcome measures included: WMFT, ARAT, SIS, Box and Block, 9 hole peg test, MAL, FIM	FMA-UE score increased on average by 3.59 (this is below the MCID (4.25-7.25). WMFT scores of pts in intervention group were significantly greater than those in control group (3 studies, n=146) 2 studies had surgically implanted VNS and 1 study had tVNS SIS (hand function), Box and Blocks and Nine-hold Peg test scores were similar in both groups.	**++**

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		-6 weeks, about 3 times per week followed by a home exercise program -30min per day for 15 days -6 weeks, 3 times per week for total of 18 sessions followed by home exercise programme	studies of invasive VNS were the same – burst of 500ms with constant current of 0.8mA, pulse duration 100us and frequency 30 Hz. Stimulation sight – left vagus nerve Stimulation site for tVNS was left external acoustic meatus. Stimulation parameters were adjusted independently to a pulse duration of 0.3ms, frequency 20Hz, repeated every 5 min for 60 sec		Adverse events: invasive VNS vs control – no significant difference associated with device implantation. One pt reported skin redness in the tVNS at point of contact with electrodes Conclusion: VNS paired with rehabilitation is a promising strategy to promote UL recovery	
492	K. Zhao et al (2021). 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.	A systematic review and meta-analysis . Five RCTs , 178 participants of acute , subacute & chronic stroke participants : (One study: subacute or chronic; one study subacute or chronic; three studies : chronic phase of stroke) Two independent reviewers. PEDro score used to determine quality (Mean score 8) Risk of bias assessment undertaken	The effect of Vagus Nerve Stimulation (invasive and non-invasive) paired with rehabilitation on UL recovery compared with Rehabilitation or sham VNS and rehab . 2 studies used non-invasive VNS & 3 studies used surgically implanted VNS. Intervention ranged from 10days to 6 weeks. Stimulation parameters of VNS,	Primary Outcome: Fugl-Meyer assessment for upper extremity score (FMA-UE) ; secondary outcomes : Wolf Motor Function test score ; Stroke Impact Scale (hand function);Box and Block Test and Nine hole peg test. Outcomes were measured at baseline & at end of intervention. Adverse events were also reported.	FMA-UE scores increased as result of VNS with rehabilitation when compared to rehabilitation with or without sham VNS . (M.D =3.59;95% CI,2.55-4.63,P<0.001) . Wolf Motor Function Test : 2 studies showed significant difference between invasive VNS & control group (mean difference =0.30;95% CI . 0.18-0.43 P,0.01) .One study showed difference in variation of score between non-invasive TNS & control group (MD=3.59;95% CI,1.97-5.21; P<0.01)	+ Good quality SR & MA but small number of studies and participants. Lacked detail on type and nature of rehabilitation. Outcomes measured immediately after invention with no long term follow up.

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			varied between studies of invasive versus non invasive : Invasive : Current 0.8Ma, pulse duration 100 µs, frequency 30Hz at burst of 500ms) Non invasive: Pulse duration of 0.3ms,freq of 20Hz repeated every 5min for 60min)		No significant difference in Stroke Impact Scale , Box and Block Test or Nine Hole peg test. No adverse events reported with invasive VNS . Of the two non invasive VNS studies, one study reported one participant developing skin redness of point of contact with electrodes.	
488	J. Dawson et al (2021). Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. The Lancet. 397: 1545-1553.	Setting: Multi-centre, neurorehab centres UK/USA Design: randomised, triple-blind, sham-controlled trial. ITT analysis Subjects: 108 stroke patients (FMUE 20-50; age 22-80; 9 months to 10 years post-stroke randomised – 53 to VNS, 55 to control.	6 weeks rehabilitation + real VNS (VNS group) or + sham VNS (control group). Rehabilitation = three times per week; total of 18 sessions. In sessions - high-repetition (<300), task-based, functional, individualised, and progressive upper limb exercises	Oms at start, end and +90 days after treatment stopped Primary outcome was change in FMUE at end of 6 weeks rehabilitation. FMUE also measured at 90 days after treatment. Secondary outcomes: Wolf Motor Function Test (WMFT; function and time score), Motor Activity Log (MAL), Stroke Impact Scale (SIS) score, Stroke Specific Quality of Life (SS-QOL), EQ-5D, and the Beck Depression Inventory (BDI).	Mean FMA-UE score increased by 5·0 points (SD 4·4) in the VNS group and by 2·4 points (3·8) in the control group (between group difference 2·6, 95% CI 1·0–4·2, p=0·0014). 90 days after in-clinic therapy, a clinically meaningful response on the FMA-UE score was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the control group (between group difference 24%, 6–41; p=0·0098).	++ Comment: training looks like GRASP and targeting 'activity' so why not ARAT or WMFT as outcome measure (or not do task specific training).
488	J. Dawson et al (2021). Vagus nerve stimulation paired with rehabilitation for	Multi-centred, randomised sham-controlled trial (n=108). Triple blind.	All participants were implanted with a vagus nerve	The primary outcome was change in FMA-UE score from baseline to the first day following completion	On the first day after completion of in-clinic therapy, the mean FMA-UE score increased by 5·0 points	++ Very well conducted study

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	upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. The Lancet. 397: 1545-1553.	Study participants were adults between 22 years and 80 years, with a history of unilateral supratentorial ischaemic stroke that occurred between 9 months and 10 years before enrolment. People with moderate-to-severe arm impairment defined as an FMA-UE score of 20–50 were eligible for inclusion	stimulation device. The VNS group (n=53) received 0·8 mA, 100 µs, 30 Hz stimulation pulses, lasting 0·5 s. The control (sham) group (n=55) received 0 mA pulses. All participants received 6 weeks of in-clinic therapy (three times per week; total of 18 sessions) followed by a home exercise programme. In-clinic rehabilitation was well reported and all attempts were made to ensure as much standardisation as possible between groups.	of in-clinic therapy. The secondary outcomes measures were clinically meaningful response on FMA-UE score at day 90; change in day 90 WMFT-Functional score relative to pre-treatment (baseline); and change in day 90 FMA-UE score relative to baseline. (Clinically meaningful response as a 6-point or greater improvement in FMA-UE score) Tertiary outcome measures were the MAL score, SIS score, SS-QOL score, and EQ-5D score.	(SD 4·4) in the VNS group and by 2·4 points (3·8) in the control group (between group difference 2·6, 95% CI 1·0–4·2, p=0·0014). 90 days after in-clinic therapy, a clinically meaningful response on the FMA-UE score was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the control group (between group difference 24%, 6–41; p=0·0098). There was one serious adverse event related to surgery (vocal cord paresis) in the control group.	Every attempt made to minimise potential bias; Triple blind, use of sham, good reporting of randomisation, same blinded assessor for baseline and follow up assessments. Adequately powered.
490	J. Wei et al (2020). The effect of VNS on the rehabilitation of stroke: A meta-analysis of randomized controlled studies. Journal of Clinical Neuroscience. 81: 421-425.	Systematic review and meta-analysis of randomized controlled trials on adults with stroke using the random-effect model. 2 indep reviewers and Jadad scale used for quality	VNS plus upper limb rehabilitation versus rehabilitation	Primary outcome = Fugl-Meyer (FMA-UE). Secondary outcomes = Wolf Motor Function Test, Box and Block Test, Nine-Hole Peg Test, atrial fibrillation and adverse events	Three RCTs included. Total sample size =49. VNS improved UL Impairment (FMA-UE SMD= 3.86; 95%CI = 1.19 to 6.52; P = 0.005) and function (WFMT SMD =0.33; 95%CI = 0.04 to 0.62; P = 0.03), but not Box & Block (SMD = -0.31; 95%CI = -3.48 to 2.86; P = 0.85), 9-Hole Peg Test (SMD =8.35; 95% CI= -40.59 to 57.28; P = 0.74), atrial fibrillation (RR= 3.46; 95%CI= 0.39 to 30.57; P= 0.26)	**++** Good quality review but small scale – only 3 trials and 49 participants. Conclusions: VNS plus upper limb rehabilitation appears safe and to improve upper limb impairment and possibly UL function, compared to standard rehabilitation alone.

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					or adverse events (RR= 0.59; 95%CI= 0.21 to 1.61; P= 0.30). Conclusions: VNS may be beneficial to the rehabilitation of stroke	
490	J. Wei et al (2020). The effect of VNS on the rehabilitation of stroke: A meta-analysis of randomized controlled studies. Journal of Clinical Neuroscience. 81: 421-425	Systematic review and meta-analysis of randomised controlled trials. Only two terms were used – "VNS" and "Stroke". Quality of trials assessed using Jadad scale (0-5 points – 0-2=low quality, 3-5=high quality).	Only randomised controlled trials investigating vagus nerve stimulation with rehabilitation versus rehabilitation only in stroke were included. Any form of vagal nerve stimulation seems to have been included.	Primary outcome was described as Fugl-Meyer Assessment – upper extremity (FMA-UE). Secondary outcomes include Wolf Motor Function Test (WMFT), Box and Block Test (BBT), Nine-Hole Peg Test (NHPT), atrial fibrillation and adverse events.	Three papers identified including 49 participants in total. Primary outcome measure – FMA-UE-SMD=3.86 (95%CI=1.2 to 6.5). p=0.005 Secondary OM's WMFT-SMD=0.33 (95%CI=0.04 TO 0.6). p=0.03 BBT=-SMD=-0.31 (95%CI=-3.5 to 2.9). NHPT=8.35s (95%CI=-40.6 to 57.3) AF=Risk ratio=3.46 (95%CI=0.4 to 30.6) Adverse events=Risk ratio=0.59 (95%CI=0.21 to 1.61)	**++** Good quality review. In the discussion, there was acknowledgment that there was a variety of techniques to stimulate the vagus nerve but it was not clear what form the three studies included used.
487	J. Dawson et al (2020). Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Stroke: One-Year Follow-up. Neurorehabilitation and Neural Repair. 34: 609-615.	People with moderate to severe chronic stroke 17 participants were implanted and randomised, 8 to active VNS and 9 to Control VNS and underwent 6 weeks of in clinic therapy with control or active VNS followed by home exercises through day 90.	Control group received intense in-clinic paired VNS rehabilitation followed by all participants then performing an individualized home exercise programme with self-administered VNS for 30 minutes.	Fugl-Meyer UE, WMFT, Box and Block Test, Nine - hold Peg Test, SIS and MAL	From the original paper: There were three serious adverse events related to implantation surgery including one implantation wound infection requiring treatment with intravenous antibiotics but resolved, one case of shortness of breath and dysphagia, likely due to intubation, which recovered,	**-** Small sample size In this paper participants and investigators were unblinded This paper reported on 1 year safety, feasibility, adherence and outcome data from the

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		The participants and investigators were then unblinded. The control VNS group then received 6 weeks in clinic active VNS. All participants then performed an individualised home exercise programme with self-administered Active VNS This paper reports on the second unblinded phase.	In-clinic participants received between 300-500 discrete stimulations to the vagus nerve per visit paired with task specific movement. Session was 90 minutes and participants did 18 sessions (27 hours).		and one case of hoarseness due to vocal cord palsy. No VNS treatment related serious adverse events during the long-term therapy. Home based VNS combined with rehab therapy is feasible and safe. There were 2 dropouts. On average participants performed 200 home therapy sessions (57.4% of home days available). 1 year after randomization the FMA-UE score increased by 9.2 points. Other functional measures also improved at 1 year.	original study which was randomized and double blind.
487	J. Dawson et al (2020). Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Stroke: One-Year Follow-up. Neurorehabilitation and Neural Repair. 34: 609-615.	Setting - Four centres (three in US and one in UK) Design - double-blind randomised study for 90 days. After 90 days the control group received 6 weeks of treatment. All patients followed up for one year from initial study. Subjects - Between four months and five years post stroke with a FMA-UE between 20 and 50. Mean age=61 years (+/-9.6 years). 17 participants recruited (8 in treatment and 9 in control).	Implantable VNS device in all 17 participants. Treatment group received VNS and intense rehabilitation. Control group received no VNS and intense rehabilitation. Rehabilitation session lasted about 2 hours with additional home exercise programme. VNS – stimulation every 10 seconds for 30 minutes.	This is a follow-up paper so outcome measures for this paper are presented for 6, 9 and 12 month follow-up. These outcome measures were not blinded. FMA-UE, WMFT, BBT, NHPT, SIS and motor activity log (MAL).	15 of 17 participants included in results. Results include participants from both treatment and placebo groups following cross-over. FMA-UE 6months- 9.1 (5to13.2), 9 months- 10.7 (6.3to15.1,) 12 months- 9.2 (4.7to13.7) WMFT – Functional 6 months – 0.3 (0.1 to 0.5) 9 months – 0.2 (0.1 to 0.4) 12 months – 0.3 (0.1 to 0.6) WMFT – Timed 6 months - -6.2 (-11.3 to -1.2) 9 months - -5.1 (-10.2 to 0)	Since the results were unblinded I decided to use the SIGN cohort study checklist rather than RCT. Using this, the study can be described as high quality. There was good description about those that were lost to assessment.

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					12 months - -4.3 (-10.2 to 1.5) SIS – 6 months – 24.7 (16.6 to 33.5) 9 months – 21.7 (14.4 to 29) 12 months – 17.7 (6.5 to 28.8) MAL – 6 months – 0.7 (0.2 to 1.2) 9 months – 0.8 (0.2 to 1.4) 12 months – 0.8 (0.3 to 1.3) BBT – 6 months – 2.7 (-1 to 6.3) 9 months – 3.0 (-1.4 to 7.3) 12 months – 3.0 (-0.9 to 7.0) NHPT 6 months - -15.3 (-46.1 to 15.5) 9 months - -11.2 (-52.7 to 30.3) 12 months - -15.3 (-55.1 to 24.6) Safety - No VNS related serious adverse events between 90 days and one year. Possible AE of hiccups reported in one participant.	
703	Liu et al (2022). Effect of Combined Vagus Nerve Stimulation on Recovery of Upper Extremity Function in Patients with Stroke: A Systematic Review and	SR and MA of RCTs assessing the effectiveness of vagus nerve stimulation (VNS) plus therapies on upper limb activity following PRISMA guidelines and the Cochrane risk of bias tool. Data Sources: PubMed,	Invasive or transcutaneous VNS plus other 'Rehabiltation therapies'. No details of how these are defined (presumably	Upper limb impairment using the Fugl-Meyer Assessment—Upper Extremity (FMA-UE). Secondary outcomes = activity (Wolf Motor function test(WMFT) and	Five good quality RCTs involving 178 patients (VNS = 871) were included. A small (below clinical significance) significantly greater improvement in upper limb impairment was seen	Conclusions: VNS plus rehabilitation therapies may improve upper limb outcomes after stroke Methodologically good quality but lack of information about

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	Meta-Analysis. *Journal of Stroke and Cerebrovascular Diseases* 31:6 106390	Cochrane Library, Web of Science and Embase up to 31 July 2021 with data extracted independently by two authors.	usual care physio and/or OT). No details of control groups (probably usual care)	Motor Activity log, MAL); quality of life (Stroke Impact Scale, SIS) and adverse events	immediately after treatment (MD 3.31; 95%CI 2.33 to 4.29; p < 0.0001), which was also seen at follow up in 3 trials (MD = 3.13; 95%CI 1.47 to 4.79; p < 0.0001). No difference was seen in WMFT (MD = 1.40; 95%CI 0.86 to 3.66 p= 0.22 3 RCTs with 146 patients) but the MAL shoed greater improvement with VNS [plus therapy) in 2 trials (118 participants) (MD = 0.36; 95%CI 0.02 to 0.70; p = 0.04). SIS showed greater improvement in 2 RCTs with 120 participants (MD=5.00; 95%CI 0.08 to 9.92; p = 0.05). No difference in risk of adverse outcomes was seen (RR= 1.61; 95%CI 0.65 to 3.99; P = 0.30).	what the 'rehabilitation therapies' and controls were. Although It has been published more recently it covers the same trials as other reviews (I think) and seems less comprehensive. We could add it to the list of references)