Clinical Efficacy of Auricular Vagus Nerve Stimulation in the Treatment of Chronic and Acute Pain – A Systematic Review and Meta-Analysis

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Suppl. Tab. 1 Jadad-scale [42] and evaluation of scientific validity (developed according to [43–45]) [40].

JADAD scale			
Was the study described as randomized?		Yes/No	+1/+0
If the method of generating the sequence of randomization was described, was it adequate?		Yes	+1
If the method of generating the sequence of randomization was described, was it inadequate?		Yes	-1
Was the study described as double-blind?		Yes/No	+1/+0
If the method of blinding was described, was it adequate?		Yes	+1
If the method of blinding was described, was it inadequate?		Yes	-1
Was there a description of withdrawals and drop-outs?		Yes/No	+1/+0
Evaluation of scientific validity			
Endpoint	Are the selected endpoints relevant for the researched indications?	Yes/No	+1/+0
Follow-Up/ Duration of use	Is the duration of follow-up sufficient to evaluate the effect of duration of use of the intervention on outcome/complications, respectively to identify complications.	Yes/No	+1/+0
Statistical method	Are the statistical analysis methods described and adequate?	Yes/No	+1/+0
Clinical significance	Is the observed efficacy of the intervention clinically/statistically significant?	Yes/No	+1/+0

Suppl. Tab. 2 Results of the evaluation on quality and level of evidence of the included studies – chronic pain. RCT – randomized controlled trial. Extended from [40].

Chronic Pain								
Author	**Method**		**Scientific Validity**		**Total Score**			**Type of Study & Level of Evidence**
	JADAD 1	**JADAD 2**	**Validity 1**	**Validity 2**	**Sum 1**	**Sum 2**	**Ø**	
1. Sator-Katzenschlager 2003 [60]	5	5	4	4	9	9	9	RCT; **Ib**
2. Sator-Katzenschlager 2004 [58]	5	5	4	4	9	9	9	RCT; **Ib**
3. Kong and Ng 2009 [56]			2	2	2	2	2	Case-Series; **V**
4. Napadow 2012 [53]	2	2	3	3	5	5	5	Random. Cross-Over; **IIa**
5. Straube 2015 [57]	3	4	4	4	7	8	7.5	RCT; **Ib**
6. Sacco 2016 [68]			4	3	4	3	3.5	Retrospect. Cohort; **III**
7. Kovacic 2017 [50]	5	5	4	4	9	9	9	RCT; **Ib**
8. Grolaux 2019 [49]			2	1	2	1	1.5	Case-Series; **V**
9. Krasaelap 2019 [51]	5	4	4	4	9	8	8.5	RCT; **Ib**
10. Mion 2020 [52]			3	3	3	3	3	Case-Series; **V**
11. Kutlu 2020 [66]	3	2	3	3	6	5	5.5	RCT; **Ib**
12. Shi 2021 [70]	3	3	4	4	7	7	7	RCT; **Ib**
13. Széles 2021 [61]			4	4	4	4	4	Retrospect. Cohort; **III**
14. Aranow 2021 [65]	5	5	4	4	9	9	9	RCT; **Ib**
15. Woodbury 2021 [67]	3	3	3	3	6	6	6	Case-Control; **III**
16. Marsal 2021 [64]			4	4	4	4	4	Case-Series; **V**
17. Zhang 2021 [36]	3	3	4	4	7	7	7	RCT; **Ib**
18. Feng 2022 [55]			4	4	4	4	4	Case-Series; **V**

19. Courties 2022 [63]			3	2	3	2	2.5	Case-Series; **V**
20. Santucci 2022 [54]			4	4	4	4	4	Case-Series; **V**
21. Li 2022 [69]	3	3	2	2	5	5	5	RCT; **Ib**
22. Ünal 2022 [59]	3	3	2	2	5	5	5	RCT; **Ib**
23. Uzlifatin 2023 [62]	2	2	3	2	5	4	4.5	RCT; I**b**

Suppl. Tab. 3 Results of the evaluation on quality and level of evidence of the included studies – acute postoperative pain. RCT – randomized controlled trial. Extended from [41].

Acute Postoperative Pain								
Author	**Method**		**Scientific Validity**		**Total Score**			**Type of Study & Level of Evidence**
	JADAD 1	**JADAD 2**	**Validity 1**	**Validity 2**	**Sum 1**	**Sum 2**	**Ø**	
1. Sator-Katzenschlager 2006 [73]	4	5	4	3	8	8	8	RCT; **Ib**
2. Likar 2007 [77]	5	5	3	3	8	8	8	RCT; **Ib**
3. Michalek-Sauberer 2007 [79]	4	4	3	2	7	6	6.5	RCT; **Ib**
4. Kager 2009 [78]	3	3	4	4	7	7	7	RCT; **Ib**
5. Holzer 2011 [71]	4	5	2	2	6	7	6.5	RCT; **Ib**
6. Tsang 2011 [72]	4	4	3	3	7	7	7	RCT; **Ib**
7. Chakravarthy 2019 [15]	2	2	3	3	5	5	5	Case-Control; **III**
8. Ahmed 2021 [74]			3	2	3	2	2.5	Case-Control; **III**
9. Blank 2021 [75]	5	5	4	3	9	8	8.5	RCT; **Ib**
10. Chelly 2022 [76]			4	4	4	4	4	Case-Series; **V**
11. Ilfeld 2022 [81]			3	3	3	3	3	Case-Series; **V**
12. Zhou , 2022 [80]	5	5	4	4	9	9	9	RCT; **Ib**

Suppl. Tab. 4 Results of the evaluation on quality and level of evidence of the included studies – acute experimental pain. Extended from [41].

Acute/Experimental Pain								
Author	**Method**		**Scientific Validity**		**Total Score**			**Type of Study & Level of Evidence**
	JADAD 1	**JADAD 2**	**Validity 1**	**Validity 2**	**Sum 1**	**Sum 2**	**Ø**	
1. Busch 2013 [82]	4	5	3	3	7	8	7.5	Random. Cross-Over; **IIa**
2. Laqua 2014 [86]	2	2	3	3	5	5	5	Random. Cross-Over; **IIa**
3. Frokjaer 2016 [85]	3	3	3	3	6	6	6	Random. Cross-Over; **IIa**
4. Usichenko 2017 [87]	2	2	2	1	4	3	3.5	Random. Cross-Over; **IIa**
5. Janner 2018 [84]	3	2	3	3	6	5	5.5	Random. Cross-Over; **IIa**
6. Farmer 2020 [83]	3	2	3	2	6	4	5	Random. Cross-Over; **IIa**
7. Dumoulin 2021 [88]			2	2	2	2	2	Random. Cross-Over; **IIa**

Suppl. Tab. 5 Summary and analysis of studies of aVNS in chronic pain, acute post-surgery pain and acute experimental pain (long version). Extended from [41].

Publication	Indication	Method	No. of Patients (Dropouts)	Treatment Parameters	Treatment Period	Primary Results	Secondary Results	Adverse Events
Chronic Pain								
Sator-Katzen-schlager 2003	chronic cervical pain	pVNS: 2 x Antitragus, Fossa triangularis; right or left vs. Sham-pVNS: inactive device	*n=23* pVNS=10 (1) Sham-pVNS=11 (1)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	48h/week for 6 weeks Follow-Up at 4 weeks	significant reduction of **VAS** (pVNS vs Sham, p<0.05) significant reduction was maintained up to **4 week follow-up** (p<0.05)	**psychological well-being, activity**, and **sleep** were significantly improved (pVNS vs Sham) **consumption of rescue medication** was significantly less pVNS vs Sham	no treatment-related AEs reported
Sator-Katzen-schlager 2004	chronic back pain	pVNS: Anthelix, Fossa triangularis, Antitragus; right or left vs. Sham-pVNS: inactive device	*n=61* pVNS=29 (2) Sham-pVNS=26 (4)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	48h/week for 6 weeks, Follow-Up at 3 months	significant reduction of **VAS** (pVNS vs Sham, p<0.05) significant reduction was maintained up to **3 months of follow-up** (p<0.05)	**psychological well-being, activity,** and **sleep** were significantly improved (pVNS vs Sham) **consumption of rescue medication** was significantly less pVNS vs Sham	no treatment-related AEs reported
Kong and Ng 2009	chronic pain (spondylosis, migraine)	pVNS: 3 points either Fossa Triangularis, Crus Superius Anthelicis, Antitragus, Crus Inferius Anthelicis, or Concha; right or left	*n=9* (migraine n=2, spondylosis n=7) pVNS=6 (3)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	4d/week for 2 weeks Follow-Up at 2 weeks	mean VAS reduction from 7 (baseline) to 4 (week 1), 2 (week 2) and 3 (week 4) improvements were maintained for up to 2 weeks after completion of treatment	n.a.	8 mild AEs: local pain at stimulation site (3), nausea (2),dizziness (1), local itch (2)

Napadow 2012	chronic pelvic pain (CPP/endometriosis)	tVNS (respiratory-gated): Cymba Concha, between Antihelix and Cavum Concha, left vs. Sham-tVNS (not Respiratory-gated): Earlobe, left	*n=18* tVNS=15 (3)	Cefar Acus II (Cefar Medical) rectancular, 30 Hz, 0.45 ms, amplitude below pain/discomfort threshold, stimulation duration of 0.5 s respiratory-gated/non-respiratory gated	30 minutes	trend for reduced evoked pain intensity and temporal summation of mechanical pain (respiratory-gated tVNS vs non-respiratory-gated Sham-tVNS)	no significant changes or differences on NRS scale significant **reduction of anxiety** vs baseline ($p<0.01$) and vs sham-tVNS ($p<0.05$)	not reported
Straube 2015	chronic migraine	tVNS (25 Hz): Cymba Concha, left vs. tVNS (1 Hz): Cymba Concha, left	*n=46* tVNS (25 Hz)=22 (2) tVNS (1 Hz)=17 (5)	NEMOS (Cerbomed) rectangular, biphasic, 25 Hz or 1 HZ (control group), 0.25 ms, amplitude at pain/discomfort threshold 30s ON/30s OFF	4h/day for 3 months	significantly larger reduction in **headache-days/28 days** in tVNS (1 Hz) group vs. tVNS (25 Hz) group ($p=0.035$)	number of responders 29.4% vs 13.6 % 1 Hz vs. 25 Hz), per protocol analysis no significant changes in headache intensity compared to baseline for 1 Hz vs 25 Hz group no. of days with intake of acute **headache medication, MIDAS and HIT-6 scores** were significantly reduced in both treatment groups, no inter-group differences	mild or moderate pain, paresthesia, or pruritus during or after stimulation, erythema, ulcer or scab treatment-related AEs: n=112 (n=76 in 25 Hz/n=39 in 1 Hz)
Sacco 2016	Chemotherapy-Induced Peripheral Neuropathy	pVNS: Fossa Triangularis, Tragus, Antihelix and/or Concha	n=58 pVNS=58 (0) primary endpoint =18 secondary endpoint=32 (8)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	5d/week for 5 weeks on average	significant change of 5 points (median) in **NRS** score vs baseline ($p<0.001$)	59% of patients reported marked improvements, 12.5% reported notable, yet minimal, reductions of pain and numbness, 29% non-responder effect of treatment was sustainable in all responders functional improvements in ADL, gait and balance was reported 6 patients reduced/stopped pain medication	stimulation not tolerated (1)

Kovacic 2017	chronic abdominal pain adolescents 11-18 years	pVNS: Earlobe, Fossa triangularis/Crus Superius Antihelicis, Concha (posterior), temporal region (not auricle) vs. Sham-pVNS: inactive device	*n=115* pVNS=57 (3/FU7) Sham-pVNS=47 (8/FU4)	Neuro-Stim, Innovative Health Solutions I-H-S rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2 V constant, 2h ON/2h OFF	5d/week for 4 weeks follow-up at 8-12 weeks additional questionaire 6-12 months after end of treatment	after 3 weeks: greater reduction in worst pain, **median PFSD** (pVNS vs sham, p<0.0001) these effects were sustained at extended **follow-up** (pVNS vs sham)	FDI scores: no improvements in sham group baseline vs extended FU **FDI** scores: significant improvement in pVNS group vs baseline; decrease from moderate to minimal disability range; improvement by an average of 36% no changes in STAI-C in both groups	ear discomfort (pVNS/Sham n=3/3), adhesive allergy (pVNS/Sham n=3/2),syncope due to needlephobia (pVNS/Sham n=0/1)
Grolaux 2019	IBS pain and chronic pain	tVNS: Concha, left vs. Sham-tVNS: inactive device	n=6 tVNS=6 [IBS=3, chron. pain=3] (0)	TU7000 (Digital TENS, RMP) rectangular, biphasic (CP: 5 Hz, 0.2 ms/IBS: 3 Hz, 0.25 ms), above sensory threshold (~0.8 mA)	30 minutes 2x/week for 4 weeks Follow-up after 2 months	no significant changes in BPI questionnaire clinical improvement (IBS-SSS) in IBS-patients reported	n.a.	neckpain (n=6), itch at stimulation site (n=2), nausea (n=2), headache (n=3)
Krasaelap 2019	IBD pain	pVNS: Earlobe, Fossa triangularis, Cymba Concha vs. Sham-pVNS: inactive device	n=50 pVNS=27 (0) Sham-pVNS=23 (0)	Neuro-Stim, Innovative Health Solutions, I-H-S rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V constant, 2h ON/2h OFF	5d/week for 4 weeks	59% of patients receiving active therapy compared with 26% of patients receiving sham showed ≥30% reduction in **worst abdominal pain** (baseline vs. 3 weeks of therapy, p=0.024)	after 3 weeks of treatment: lower **composite pain score** pVNS vs sham (p=0.026) lower **usual pain score** pVNS vs sham (p=0.029) **global symptom** improvement pVNS vs sham (p<0.001)	allergic reaction to adhesive (n=1)
Mion 2020	IBS pain	tVNS: Concha, left	n=12 tVNS=9 (3)	Urostim (Schwa Medico) rectancular, 30 Hz, 0.25 ms, 0.5-20 mA (below sensory threshold)	3h/day for 5d/week for 6 months	significant **decrease of the IBS-SSS** at 3 (p=0.0084) and 6 months (p=0.0209) vs baseline clinical significant response (decrease of at least 30% of the IBS-SSS) was present in 5 patients at 3 months (2 IBS-D and 3 IBS-C), and in 4 at 6 months (2 IBS-D and 2 IBS-C)	**severity and frequency of abdominal pain** were significantly decreased after 1 month until end of study (6 monhths, p<0.03) vs baseline no significant changes in QoL-SF36, psychological wellbeing - PANAS, STAI, CES-DS, PSS, WCC; inflammatory cytokines and fecal calprotectin	none

							co-medication (e.g. laxative drugs, antispasmodics) were reduced in in several cases	
Kutlu 2020	Fibromyalgia	exercise + tVNS: Tragus and Concha, bilateral vs. exercise	*n=60* tVNS + exercise=27 (3) exercise=25 (5)	TENS device biphasic, asymmetrical, 10 Hz, 0.5 ms, amplitude at sensory threshold	30 min/day for 5d/week for 4 weeks	both groups had statistically significant improvements in **pain (VAS), depression (Beck Depression Scale), anxiety, functionality, and life quality scores (SF-36)** vs baseline non-significant improvements tVNS vs control	n.a.	none
Shi 2021	IBS-C, chronic pelvic pain	tVNS: Cymba Concha, bilateral vs. control (non-auricular stimulation): Elbow, bilateral	*n=42* tVNS=21 (0) control (Elbow)=19 (2)	SNM-FDC01 (Ningbo Maida Medical Device Inc.) rectangular, 25 Hz, 0.5 ms, 0-2 mA (at pain/discomfort threshold), 2s ON/3s OFF	2x30 minutes/day for 4 weeks	significant increase **CSBMs/week** tVNS vs sham (p=0.001) and significant decrease of **VAS** in abdominal pain tVNS vs sham (p=0.001)	tVNS vs sham: improved **quality of life** (p=0.020), decreased **IBS-SSS** (p=0.001) improved **rectoanal inhibitory reflex** (p=0.014), improved **rectal sensation** (p<0.04); decreased a number of proinflammatory cytokines and serotonin enhanced **vagal activity** (EKG, p=0.040)	none
Széles 2021	treatment-resistant chronic back pain	pVNS: Cymba Concha, Concha, Crus Anthelicis, left and right alternating	*n=148* pVNS=148 (0)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	4d/week for at least 3 weeks	≥30% reduction in average **NRS** pain intensity (ITT): 51.4% (week 1), 70.3% (week 3), 72.3% (week 6), 75.0% (3 months) ITT population: 32.4% of all patients exhibited a ≥ 50% improvement of average NRS pain intensity (definition of responder) (week 1), 49.3% (week 3), 58.8% (week 6)	subjective well-being improved by 1.89 points (±1.66; n=54) 49.3% reduced or discontinued pain medication (n=67) improved mobility (n=20),improved quality of sleep (n=3), reduced anxiety (n=1)	unwanted device disconnectin (n=20), unwanted disruption of stimulation at some point (n=15), skin irritation (n=4), dizziness/headache/pain at stimulation site (n=1)

Aranow 2021	SLE and musculoskeletal pain	tVNS: Concha (anterior and posterior) vs. Sham-tVNS: Earlobe, inactive device	*n=18* tVNS=12 (0) Sham-tVNS=6 (0)	TENS 7000 (Roscoe) rectangular, 30 Hz, 0.3 ms, amplitude at pain/discomfort threshold	5min/day for 4 days	significant decrease in **pain** and **fatigue** tVNS vs sham	PtGA, joint counts and PGA also improved tVNS vs sham responses were maintained through day 12 plasma levels of **substance P** were significantly reduced tVNS vs baseline	none
Woodbury 2021	Fibromyalgia	pVNS: Concha (posterior), Crus Helicis, Crus Superius Anthelicis, Earlobe; right or left vs. Standard-of-care	*n=21* pVNS=12 (0) Control=9 (0)	NSS (EAD MFS, BRIDGE, Innovative Health Solution) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V, 2h ON/2h OFF	5d/week for 4 weeks 12 weeks follow-up	nonsignificant improvement in pain scores pVNS vs control; significant improvements in **sleep**, **activity**, **mood** at week 6 pVNS vs control	Neuroimaging data displayed increased connectivity to areas of the cerebellum and executive control networks in the pVNS group vs control group following treatment	mild irritation at stimulation site (n=2)
Marsal 2021	Rheumatoid Arthritis	tVNS: Cymba Concha	*n=30* tVNS=27 (3)	Nēsos rectangular, 20 kHz, amplitude at sensory threshold (~3 mA)	30 min/day for 12 weeks Follow-Up at W1, W2, W4, W8, W12	significant mean change in **DAS28-CRP** at 12 weeks (p<0.0001) vs baseline	reduction in **HAQ-DI** (p<0.0001) vs baseline	skin abrasion (n=1); classified not treatment-related: accidental mechanical fall (n=2), mucous build-up in throat (n=1)
Zhang 2021	Migraine without Aura	tVNS: Cymba Concha, left vs. Sham-tVNS: Cauda Helicis, left	*n=63* tVNS=33 (1) Sham-tVNS=26 (3)	SDZII (Huatuo) rectangular, 1 Hz, 0.2 ms, amplitude just below pain/discomfort threshold	30 min/session, 12 sessions in 4 weeks	significantly reduced number of **migraine days** (p<0.05), **pain intensity** (p<0.01) and **migraine attack duration** (p<0.05) after 4 weeks of treatment tVNS vs sham significant reduction of **migraine days** tVNS vs baseline (p<0.001)	functional connectivity analysis revealed that taVNS can increase the connectivity between the motor-related thalamus subregion and anterior cingulate cortex/medial prefrontal cortex, and decrease the connectivity between occipital cortex-related thalamus subregion and postcentral gyrus/ precuneus	not reported

Feng 2022	Migraine without Aura	tVNS: Cymba Concha, left for fMRI: matched healthy controls	*n=60* tVNS=60 (0) Control=60(0)	SDZII (Huatuo) rectangular, 1 Hz, 0.2 ms, amplitude just below pain/discomfort threshold (1.5-5 mA)	30 min/session, 12 sessions in 4 weeks	significant changes in **VAS, attack times, total duration, MSQ, SDS, SAS** ($p<0.05$) vs baseline no significant changes in rescue medication (ibuprofen)	fMRI: changes in the right PoCG after tVNS treatment were negatively associated with corresponding reduction of VAS scores, and in the bilateral precuneus positively associated with the reduction in the attack duration	not reported
Courties 2022	Osteoarthritis/ Handpain	tVNS: Cymba Concha, left	*n=20* tVNS=18 (2)	TENSeco2 (Schwa-Medico) biphasic, asymmetric, balanced, 25 Hz, 0.05 ms, amplitude up to 15 mA or below pain/discomfort threshold	1h/day for 4 weeks	significant reduction in **VAS** tVNS vs baseline ($p=0.001$)	significant reduction in **FIHOA** ($p=0.01$) 12 patients had a reduced number of painful joints, 15 patients had a decrease in the number of swollen joints no significant changes in paracetamol consumption	ear discomfort (n=1)
Santucci 2022	chronic functional abdominal pain	pVNS: Earlobe, Fossa Triangularis/Crus Superioris Anthelicis, Concha (posterior), temporal region (not auricle)	*n=20* pVNS=19 (1)	IB-Stim (Innovative Health Solutions) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V constant, 2h ON/35min OFF	5d/week for 4 weeks	during pain evoked by WL-SPT, **VAS** ($p=0.004$) and **nausea** ($p=0.02$) were lower tVNS vs baseline significant improvements of **resting VAS** ($p=0.03$), **abdominal pain** ($p<0.0001$), **pain catastrophizing** ($p=0.0004$), **somatic complaints** ($p=0.01$), **functional disability** ($p=0.04$), and **anxiety** ($p=0.02$) vs baseline some improvements were sustained long-term (6-12 months)	improvement of **sleep** ($p<0.05$), as well as actigraphy-derived **sleep onset latency** ($p=0.03$)	not reported

Li 2022	depression with chronic pain	tVNS: Cymba Concha and electroacupuncture (EA) at parietal and frontal skin vs control: citalopram	*n=60* tVNS+EA=28 (2) citalopram=28 (2)	SDZ-IIB (Hwato) 4Hz for 5 s, 20Hz for 10 s, the sparse and dense wave alternated, amplitude below pain/discomfort threshold	2x30min/day for 5 consecutive days/week over 8 consecutive weeks	both groups had significant reductions in **depressive** and **pain symptoms** (decrease in MARDS and SF-MPQ scores)	pain intensity score (SF-MPQ): larger reduction with citalopram vs taVNS+electroacupuncture at 6 weeks (P = 0.036) higher **sleeping medication** use at week 6 in citalopram group vs taVNS+EA group (p=0.049). Otherwise no significant differences between treatment groups (SF-36, PSQI)	not reported
Ünal 2022	myofascial pain syndrome (neck)	stretching exercise + ischemic compression + tVNS: Tragus and Concha, both ears vs stretching exercise + ischemic compression	n=60 tVNS=27 (3) control=26 (4)	Vagustim (Vagustim) biphasic asymmetric, 10Hz, 0.5ms, amplitude at sensory threshold	10x30min/5 days a week for 2 weeks	both groups show significant improvements in **VAS, algometer, Jamar** vs baseline **VAS, algometer, Jamar, secretomotor** (Compass-31) statistically significant higher in tVNS + ex + IC vs exercise + IC	**SF-36** improvement in exercise + IC vs baseline; **physical function, social functionality, pain (SF-36)** improvement in exercise + IC + tVNS vs baseline	not reported
Uzlifatin 2023	chronic low back pain	tVNS + exercise: Cymba Conchae, Cavity Conchae, left vs exercise	*n=22* tVNS + exercise=11 (0) exercise=11 (0)	TENS Myoemd 632 (Enraf-Nonius) 25Hz, 0.25ms, amplitude below pain/discomfort threshold	20min/day for 5 days/week for 2 weeks	CRP: no change in exercise group vs baseline, slight increase in tVNS group vs baseline	n.a.	no AEs

Acute Postoperative Pain								
Sator-Katzen-schlager 2006	perioperative pain (Oocyte-Aspiration)	pVNS: 2 x Fossa Triangularis, Antitragus; left or right vs. Sham-pVNS 1: inactive device vs. Sham-pVNS 2 (control): needle-free electrodes, inactive device	*n=94* pVNS=32 (0) Sham-pVNS 1=32 (0) Sham-VNS 2 (control)=29 (1)	P-Stim (Biegler) rectangular, monophasic, changing/alternating polarity, 1 Hz, 1 ms, 2 mA (3.8V) constant, 3h ON/3h OFF	start 30 min before surgery until 1h after surgery	pain relief (**VAS**) was significantly greater in group p-VNS during and after the procedure as compared with both sham groups (p<0.001)	subjective **well-being** was significantly greater in pVNS group during and after the procedure (p<0.005) **consumption of the opioid** (remifentanil) was significantly lower in group p-VNS (p<0.001) patients in sham-pVNS 2 (control, needle free) were significantly more tired (p<0.001) comparable nausea in all groups	no treatment-related AEs reported
Likar 2007	postoperative pain (laparoscopic nephrectomyomie)	pVNS: Cymba Concha, Fossa Triangularis, Antitragus vs. Sham-pVNS: inactive device	*n=44* pVNS=21 (1) Sham-pVNS=20 (2)	P-Stim (modified, Biegler) rectangular, monophasic, alternating polarity, 1 Hz, 20 ms, amplitude below threshold, 3h ON/3h OFF	start 30 minutes before surgery for 96 hours	pVNS vs sham-pVNS: better **VAS at rest** and **VAS on exertion,** especially till 1h after surgery (p<0.05)	postoperative **consumption of morphine hydrochloride** was significantly less pVNS vs sham-pVNS (p<0.05) **time of first analgesic request** was significantly later pVNS vs sham-pVNS (p<0.05)	Nausea and vomiting (pVNS/Sham n=5/1)
Michalek-Sauberer 2007	postoperative pain (molar tooth-extraction)	pVNS: Earlobe, Fossa Triangularis, Cavum Concha; left or right vs. Sham-pVNS 1: inactive device vs. Sham-pVNS 2: needle-free electrodes, inactive deice	*n=128* *pVNS=48 (15) Sham-pVNS 1=26 (8) Sham-VNS 2=26 (5)*	P-Stim (modified, Biegler) rectangular, monophasic, alternating polarity, 2/100 Hz changing every 3s, 3.8V (2 mA) constant, 3h ON/3h OFF	start 30 minutes before surgery for 48 hours	the median fraction of time when pain was rated as moderate or worse did not differ significantly among the treatment groups no significant differences in perceived pain intensity	analgesic drug consumption (acetaminophen, mefenamic acid) did not differ among the groups	syncope (pVNS/Sham n=1/0), ear pain due to stimulation (pVNS/Sham n=7/2), tiredness (pVNS/Sham n=10/3)

Kager 2009	postoperative pain (Tonsill-ectomy)	pVNS: Fossa Triangularis, Antitragus, Tuberculum Auriculare vs. Sham-pVNS: inactive device	*n=33* pVNS=16 (0) Sham-pVNS=17 (0)	P-Stim (modified, Biegler) rectangular, monophasic, alternating polarity, 1 Hz, 20 ms, amplitude below sensory threshold, 3h ON/3h OFF	start 30 minutes before surgery for 96 hours	mean **VAS** was significantly lower pVNS vs sham-pVNS 9 (p=0.044), 12 (p=0.022), and 24h (p=0.045) postoperatively	sham-pVNS had a higher analgesic consumption vs pVNS (not significant)	nausea and vomiting (pVNS/Sham n=5/1)
Holzer 2011	postoperative pain (gynecological surgeries)	pVNS: Fossa Triangularis, Antitragus, 1 individual point vs. Sham-pVNS: needle-free electrodes, inactive device	*n=40* pVNS=20 (0) Sham-VNS=20 (0)	P-Stim (Biegler) rectangular, monophasic, alternating polarity, 1 Hz, 20 ms, 3.8V (2 mA) constant, 3h ON/3h OFF	start post-surgery for 72 hours	no significant differences in VAS	no significant differences in consumption of analgetics	not reported
Tsang 2011	postoperative pain (Hysterectomy)	tVNS: 2 x Fossa Triangularis, Crus Anthelicis, Helix, Antitragus vs. Sham-tVNS: Earlobe, bilateral vs. no intervention: bed rest	*n=48* tVNS=16 (0) Sham-tVNS=16 (0) control=16 (0)	IC-4107 (ITO Ltd.) rectangular, biphasic, 1 Hz, 0.05-0.15 ms, individual amplitude	90s at each stimulation point left and right	significant reduction of **VAS** tVNS vs baseline ($p<0.05$) and tVNS vs control group ($p<0.05$) no significant improvement in the performance of PEFR	n.a.	none
Chakravarthy 2019	postoperative pain (Sectio)	pVNS: Antitragus, Crus Antihelicis, Fossa Triangularis vs. standard-of-care	*n=100* pVNS=47 (3) control=49 (1)	ANSiStim (DyAnsys) rectangular, monophasic, aternating polarity, 1 Hz, 1 ms, 3.8V (2mA) constant, 3h ON/3h OFF	start about 1h post-surgery for 48 hours	**NRS pain** intensity significantly reduced pVNS vs control group requirements of supplementary analgesics were lower pVNS vs control 37 of 50 participants (pVNS) rated the acceptability of the device good, while 12 found it tolerable, and 1 found it intolerable	n.a.	device not tolerated (pVNS n=1)

Ahmed 2021	postoperative pain (Roux-en-Y gastric-Bypass)	pVNS: Tragus, Scapha, Helix (posterior), Lobule (reference electrode) vs. historical control group (standard-of-care)	*n=18* pVNS=8 (0) control=10 (0)	NSS-2 BRIDGE device (NBD; Innovative Health Solutions) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V constant, 2h ON/2h OFF	start post-surgery (post-anesthesa care unit) for 5 days	60.2% reduction in opioid consumption (milligrams of OME) at 24 hours postoperatively pVNS vs control (p=0.063) there was no difference in the requirement of pre- and intraoperative nonopiate pain medication	28% pain reduction (p=0.1) 24h postoperatively pVNS vs control no differences in PONV tolerability of the device was reported to be excellent in 7 of 8 (88%) of participants	not reported
Blank 2021	postoperative pain (colorectal surgery)	pVNS: 2 x Crus helicis, Helix (posterior), Eearlobe (reference electrode) vs. Sham-pVNS: inactive device	*n=54* pVNS=28 (0) Sham-pVNS=24 (2)	NSS (EAD, MFS, BRIDGE, Innovative Health Solutions) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2 V constant, 2h ON/2h OFF	start shortly before surgery for 5 days	no difference in OME/day pVNS vs sham-pVNS subgroup analyses: benefit for patients after **open surgery** demonstrated with significantly less **OME** (p=0.0278), also patients aged 60 to 70 and >70 years derived a benefit from active pVNS in comparison with those aged 30 to 40, 40 to 50, and 50 to 60 years old (p = 0.01092)	overall decrease in STAI nausea was not significantly different among groups differences in **daily NRS** pain scores only at day 3 postoperatively pVNS vs sham-pVNS (p=0.034) overall, participants were satisfied with the device (8.2 ± 2.6 of 10 possible points) no difference in timepoint of discharge	intractable nausea (pVNS/Sham n=2/3)
Chelly 2022	postoperative pain (kidney donor surgery)	pVNS: Tragus, Scapha, Helix (posterior), Earlobe (reference electrode); left or right vs. Standard-of-care	*n=20* pVNS=10 (0) control=10 (0)	NSS-2-Bridge (Innovative Health Solutions) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V constant, 2h ON/2h OFF	start post-surgery (post-anesthesa care unit) for 5 days Follow-Up for 7 days	75.4% reduction in **OME** (p=0.03) at 24 hrs postoperatively pVNS vs control	57% reduction in pain **NRS** (p<0.05) at 24 hr, a 73.3% difference in **NRS** pain at 48 hrs (p=0.0004) pVNS vs control no difference in non-opioid analgesics administration downward trend in PONV, reduction of ondansetron requirement pVNS vs control pVNS group transfered from post-anesthesia care unit 50% earlier than control (p=0.02)	none

							time to hospital discharge was similar in both groups	
Ilfeld 2022	postoperative pain (ambulatory orthopedic and breast surgery)	pVNS: Tragus, Scapha, Helix (posterior), Earlobe (reference electrode); left or right	*n=7* pVNS=7 (0)	NSS-2 Bridge (Masimo) rectangular, 1/10 Hz alternating every 2s, 1 ms, 3.2V constant, 2h ON/2h OFF	start post-surgery for 5 days	median of 1 (average pain) and 3 (worst pain) on NRS at day 1 and 2, 0 at day 5	only 2 patients required opioids (5-10 mg oxycodone in the first 1-2 days post-surgery)	none
Zhou 2022	rebound pain after ropivacaine single injection femoral nerve block for anterior cruciate ligament reconstruction	tVNS: Cymba Concha, Earlobe, left vs. Sham-tVNS: Earlobe, Tail of Helix, left	*n=78* tVNS=39 (0) sham-tVNS=39 (0)	TENS 7000 (Roscoe) rectangular, 30 Hz, 0.3 ms, amplitude below pain threshold, 1h ON/1h OFF	start post-surgery for 12 hours	significant lower **NRS scores** tVNS vs sham group 8h and 12h after surgery ($p<0.05$)	significant less additional **analgesics 0-12hrs post-surgery** tVNS vs sham; significantly less **sleep disturbances** tVNS vs sham post surgery; comparable surgery-related AEs of PONC and pruritis	none

Acute Experimental Pain								
Busch 2012	acute pain/experimental heat pain healthy participants	tVNS: Concha, left vs. Sham-tVNS: inactive device	*n=48* tVNS/Sham-tVNS=48 (0)	STV02 (Cerbomed) rectangular, monophasic, 25 Hz, 0.25 ms, 0.25-10 mA (individual)	2 sessions for 1 hour each	increase of mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity tVNS vs Sham-tVNS significantly **reduced pain ratings** during sustained application of painful heat tVNS vs Sham-tVNS	no relevant alterations of cardiac- or breathingactivity no clinical relevant side effects were observed during t-VNS	Slight pain (tVNS/Sham-tVNS n=2/1), pressure fealing (tVNS/Sham-tVNS n=8/6), prickling (tVNS/Sham-tVNS n=12/2), itching (tVNS/Sham-tVNS n=10/1), tickling (tVNS/Sham-tVNS n=7/2), strange feeling (tVNS/Sham-tVNS n=1/0), irritation of swallowing (tVNS/Sham-tVNS n=1/0)
Laqua 2014	acute pain/pain perception (neurometer) healthy participants	tVNS: Cavum Concha, bilateral, reference electrode on mastoid bone vs. Sham-tVNS: inactive device	*n=22* tVNS/Sham-tVNS=21 (1)	TNS SM 2MF (Schwa Medico GmbH) rectangular, biphasic, burst stimulation mode, 2/100 Hz alternating, 0.2 ms, maximum tolerable amplitude	2 sessions for 35 minutes each 5 (outcome) measurements (baseline, 15min, 30min, 40min, 60min after start of sitmulation)	no differences in pain threshold (PT) values between conditions 15 volunteers (responders) reacted with an increase in PT tVNS vs. sham-tVNS ($p<0.01$). 6 participants reported decreased PT tVNS vs. Sham-tVNS ($p<0.05$)	heart rate and blood pressure did not change during the study	syncope due to bradycardia and hypotension (tVNS/Sham-tVSN n=1/0)
Frokjaer 2016	acute pain, bowl motility healthy participants	tVNS: Cymba Concha, left vs. Sham-tVNS: Earlobe, left	*n=18* tVNS/Sham-tVNS=18 (0)	NEMOS (Cerbomed) rectangular, monophasic, 30 Hz, 0.25 ms, amplitude at strong tingling threshold (0.1-10 mA)	60 minutes stimulation with 2x10 minutes deep slow breathing	**threshold to bone pain** increased tVNS vs sham ($p=0.001$), no effect on muscle pain no effect on muscle pain	**cardiac vagal tone** increased during active t-VNS vs sham-tVNS	none

Usichenko 2017	acute pain/experimental heat pain healthy participants	tVNS: Concha, bilateral vs. Sham-tVNS: inactive device	*n=20* tVNS/Sham-tVNS=20 (0)	TENS device (self-manufactured) rectangular, 8 Hz, 0.2 ms, amplitude at strong tingling threshold (~7.6 mA)	2 sessions for 45 minutes each	no differences in general analyses on pain threshold subgroup analysis: 8 participants reacted with significantly **increased pain threshold** after tVNS vs sham-tVNS (p=0.024) 12 reacted with a **decreased pain threshold** after tVNS vs sham-tVNS (0.012)	eight participants who reacted with an elevation of pain threshold during tVNS showed a decreased fMRI signal compared to the sham stimulation in the right caudate nucleus, the vmPFC, the left anterior insula, and the left hypothalamus	not reported
Janner 2018	acute pain/experimental heat pain healthy participants	no inervention vs. tVNS: Cymba Concha, left and right vs. Sham-tVNS 1: Earlobe vs. Sham-tVNS 2: Cymba Concha, inactive device	*n=51* no intervention/tVNS/Sham-tVNS 1/Sham tVNS 2=49 (2)	PuntoBravo (Medizintechnik Rostock GmbH) rectangular, in blocks of 9 impulses, 100 Hz, 0.2 ms, 2x/s (100 Hz/2 Hz alternating frequency)	25 minutes (start 20 minutes before heat pulses) repetitive heat pulses	**pain intensity** (VAS) decreased during all interventions as compared to no intervention (p <0.001) hypoalgesic effect of tVNS exhibitis gender-specific differences	individual pain tolerance temperatures and STAI scores comparable among the study conditions	not reported
Farmer 2020	acute pain/oesophagal pain hypersensitivity healthy participants	tVNS: Cymba Concha, left vs. Sham-tVNS: Earlobe, left	Exp. 1: n_1=34 (19*) tVNS/Sham-tVNS=15 (0) Exp. 2: n_2=25 (7*) tVNS/Sham-tVNS=18 (0) *Exclusion of non-sensitizers after classification	NEMOS (Cerbomed) rectangular, 25 Hz, 0.1 ms, amplitude below pain/discomfort threshold, 30s ON/30s OFF	25 min/session Exp. 1: stimulation during acid infusion Exp. 2: stimulation after acid infusion	Exp.1: tVNS **prevented acid-induced oesophageal hypersensitivity** vs sham-tVNS (p=0.004) Exp.2: tVNS **reversed acid-induced oesophageal hypersensitivity** vs sham-tVNS (p=0.0001)	Exp.1: increase in **cardiac vagal tone** tVNS vs sham-tVNS (p=0.016) Exp.2: increase in **cardiac vagal tone** tVNS vs sham-tVNS (p=0.03)	not reported

Dumoulin 2021	acute experimental pain healthy participants	tVNS: Cymba Concha, left vs. Sham-tVNS: Earlobe, left	*Exp. 1: n_1=22* tVNS/Sham-tVNS=22 *Exp. 2: n_2=15* tVNS/Sham-tVNS=15	NEMOS (Cerbomed) rectangular, monophasic, 25 Hz, 0.25 ms, amplitude below pain/discomfort threshold, 30s ON /30s OFF	3 hours (Exp.1), 1 hour (Exp. 2)	tVNS did not appear to modulate the cerebral and behavioral aspects of somatosensory perception	n.a.	not reported

Abbreviations: ACLR – anterior cruciate ligament reconstruction; ADL – Activities of Daily Living; BPI – Brief Pain Inventory; CPM – Conditioned Pain Modulation; CSBM – Complete Spontaneous Bowel Movements; DAS28-CRP – Disease Activity Score-28 with C-Reactive Protein; FDI – Functional Disability Inventory; FIHOA - Functional Index for Hand Osteoarthritis; FU – Follow-up; HAQ-DI – Health Assessment Questionnaire Disability Index; HIT-6 – Headache Impact Test; IBS-SSS – Irritable Bowel Syndrome-Severity Scoring System; ITT – Intention-To-Treat; MIDAS - Migraine Disability Assessment; mPFC – Medial Prefrontal Cortex; MSQ – Migraine-specific QoL Questionnaire; NRS – Numeric Rating Scale; PANAS – Positive and Negative Affect Scale; PEFR – Peak Expiratory Flow Rate; PFSD – Pain Frequency-Severity-Duration; PGA – Physician Global Assessment; PoCG – postcentral gyrus; PONV – post-operative nausea and vomiting; PP – per protocol; PtGA – patient global assessment; PSS – perceived stress scale; SAS/SDS – self-rating anxiety scale/self-rating depression scale; pVNS – percutaneous vagus nerve stimulation; SCL –skin conductance level; SFG – superior frontal gyrus; STAI – State-Trait Anxiety Inventory; STAI-C – State-Trait Anxiety Inventory for Children; TENS – transcutaneous electrical nerve stimulation; tVNS – transcutaneous vagus nerve stimulation; VAS – visual analog scale; WCC – ways of coping checklist.

Underscored locations in the ear in the methods section depict vagally innervated regions.
Bold texts in the primary and secondary results section depict statistically significant changes.