HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Electrical auricular vagus nerve stimulation for pain

Systematic Review

AIHTA Decision Support Document: 138 | ISSN-online: 1998-0469

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Electrical auricular vagus nerve stimulation for pain

Systematic Review

Vienna, March 2023

Project Team

Project leader: Gregor Goetz, MSSc MPH

Authors: Ann Scott, BSc (Hons), PhD
Viktoria Hofer, MSc
Rawan Al Froukh, PharmD, BCPS, MSc*
Ning Ma, BHSc, BmaCompSc, MSc

**In cooperation with the Department of Pharmacy, Center for Drug Policy and Technology Assessment of the King Hussein Cancer Center in Jordan*

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons), MA
Internal Review: Gregor Goetz, MSSc MPH

Correspondence: Viktoria Hofer, viktoria.hofer@aihta.at
Gregor Goetz; gregor.goetz@aihta.at

This report should be referenced as follows:

Scott A, Hofer V, Al Froukh R, Ma N and Goetz G. Electrical auricular vagus nerve stimulation for pain. AIHTA Decision Support Documents No. 138; 2023. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: [HTA Core Model®, Version 4.2]. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

IMPRINT

Publisher:

HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:

Priv.-Doz. Dr. phil. Claudia Wild, managing director

AIHTA Decision Support Documents do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 138

ISSN online 1998-0469

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

Content

List of figures

List of tables

List of abbreviations

ASA.....American Society of Anesthesiologists
aVNS.....auricular vagus nerve stimulation
BAS.....Beck Anxiety Scale
BDS .....Beck Depression Scale
CI .....confidence interval
CPSP .....chronic postsurgical pain
DALY.....disability-adjusted life years
FDI .....Functional Disability Inventory
FIQ .....Fibromyalgia Impact Questionnaire
FU.....follow-up
IBS .....irritable bowel syndrome
IBS-QOL .....irritable bowel syndrome quality of life
IBS-SSS .....irritable bowel syndrome severity scoring system
IMMPACT.....Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IQR .....interquartile range
MCID .....minimum clinically important difference
MeSH.....medical subject heading
MME.....milligram morphine equivalent
MSQ.....Migraine Specific Quality-of-Life Questionnaire
NRS .....numeric rating scale
PFSD .....Pain-Frequency-Severity-Duration
RCT .....randomised controlled trial
RR.....risk ratio
SAS .....Self-Rating Anxiety Scale
SD .....standard deviation
SDS.....Self-Rating Depression Scale
SF-36.....Short Form-36
SRS .....Symptom Response Scale
SSRI.....selective serotonin reuptake inhibitor
SSS.....symptom severity scale
STAI-C .....State-Trait Anxiety Inventory for Children
TENS.....transcutaneous electrical nerve stimulation
VAS .....visual analogue scale
VNS .....vagus nerve stimulation
VRS.....verbal rating scale
WPI.....widespread pain index

Executive Summary

Introduction

Health Problem

acute and chronic pain

Pain is one of the main reasons people seek medical care. Acute pain, which has a sudden onset, short duration and an obvious cause, is a valuable survival mechanism. In contrast, chronic pain is maladaptive and persists beyond the expected healing time of injured tissues. Chronic secondary pain is usually a symptom of another condition, whereas chronic primary pain, such as fibromyalgia and irritable bowel syndrome, is a disease unto itself.

50% of patients do not receive adequate pain therapy after surgery

Less than 50% of patients undergoing surgery receive adequate postoperative pain relief. Inadequately controlled acute postoperative pain negatively affects quality of life and functional recovery and increases the risk of post-surgical complications and chronic postsurgical pain, which is pain that persists for at least three months after a surgical procedure. Chronic postsurgical pain affects up to 10% of surgical patients.

2019: pain within the last four weeks reported from 56% of Austrians older than 15 years

The prevalence of chronic widespread pain is remarkably consistent among populations, ranging from 11% to 14%. Low back pain, headache and abdominal pain are the most commonly reported pain conditions among children and adolescents, whereas musculoskeletal disorders are the more common causes of pain in older individuals. In 2019, approximately 4.1 million Austrians (56%) older than 15 years reported experiencing some degree of physical pain in the previous four weeks. The frequency of physical pain increases considerably with advancing age, rising from 42% among 15- to 29-year-olds to 74% among those older than 75 years. Chronic pain interferes considerably with functioning and wellbeing, resulting in poor general health, disability, depression and social withdrawal, a lower life expectancy and an increased risk of developing other comorbidities.

Description of Technology

auricular vagus nerve stimulation (aVNS): pain control through low-level electrical pulses

device with two main components: 1 portable stimulator & electrodes connected to the stimulator via thin cables

Neuromodulation is the manipulation of nervous system activity using either electrical or pharmaceutical agents to achieve a therapeutic benefit such as pain relief. Auricular vagus nerve stimulation (aVNS) is a non-invasive alternative to conventional invasive vagus nerve stimulation, which is associated with various unpleasant side effects related to wire implantation (infection and vocal cord paresis) and stimulation (hoarseness, voice changes and cough). aVNS devices comprise two main components: a portable stimulation unit or pulse generator and a surface or needle electrode that attaches to the outer surface of the ear and connects to the stimulator via a thin wire. The device emits low-level pulses of electrical current that are transmitted via the wire along the vagus nerve to the brain, with the aim of modulating pain. A typical daily treatment cycle encompasses three to four stimulation sessions for a total of four to five hours, with each session lasting at least one hour. The total length of aVNS treatment varies depending on the indication.

Methods

project objective: efficacy & safety of aVNS in patients with acute postoperative or chronic pain

The aim of this report was to assess the safety and effectiveness of aVNS, compared with sham treatment or usual care, in the following two patient populations:

- Population One: Patients with **acute postoperative pain;**
- Population Two: Patients with **chronic pain.**

systematic search in 4 databases

study selection, extraction & quality assessment

A systematic search was conducted to identify relevant randomised controlled trials and systematic reviews published in English or German. The following databases were searched on 7th December 2022: Medline, Embase, The Cochrane Library and the International HTA Database (International Network of Agencies for Health Technology Assessment). Study selection, data extraction and quality appraisal were carried out independently by two authors. Any disagreements were resolved by a third author. The quality of the included studies was assessed using the Cochrane Risk of Bias 2 tool and the strength of the evidence was rated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) schema.

Domain effectiveness

effectiveness: decision-relevant endpoints

The following effectiveness-related outcomes were used as evidence to derive a recommendation:

- Population One: Pain, analgesia consumption and use of rescue medication;
- Population Two: Pain, physical functioning and symptom severity.

Domain safety

safety: decision-relevant endpoints

Device-related adverse events were used as evidence to derive a safety recommendation for both populations.

Results

Available evidence

10 RCTs: 4 for population 1 6 for population 2

Ten randomised controlled trials (RCTs) met the inclusion criteria for this report: four on acute postoperative pain and six on chronic pain.

Clinical effectiveness

Population 1: outcomes for patients with acute postoperative pain

Population One: Acute postoperative pain

The active and sham treatments were used in addition to standard care in all four RCTs. The risk of bias in the studies ranged from low to high, with only one study rated as having a low risk of bias.

no statistically significant (s.s.) differences of aVNS vs. sham treatment or ear acupuncture after planned caesarean section, surgical molar removal or colorectal surgery

The combination of percutaneous aVNS with standard of care showed no statistically significant differences in pain scores, analgesic use, or use of rescue medication after a planned Cesarean section or surgical wisdom tooth extraction, compared with sham treatment in combination with standard of care or standard of care alone. Similar results were observed in two other RCTs comparing percutaneous aVNS with ear acupuncture over a 2- to 5-day treatment cycle in patients after major colorectal surgery or wisdom tooth extraction surgery. In addition, one of these studies showed no differences

between active neurostimulation and ear acupuncture in the occurrence of postoperative nausea and vomiting, length of hospital stay or 30-day readmission rates.

One RCT evaluated the effects of transcutaneous aVNS on the relief of rebound pain after femoral nerve block in patients undergoing anterior cruciate ligament reconstruction (ACL). In patients who received aVNS in the first twelve hours after surgery, rebound pain was less frequent (18% vs. 41%; p=0.03) and lasted a shorter time (p=0.002). The consumption of analgesics (p=0.02), use of rescue medication (p=0.004) and likelihood of sleep disturbances (p=0.03) in the first 12 hours after the operation were also significantly lower after aVNS, compared with sham treatment.

1 RCT: anterior cruciate ligament (ACL) reconstruction: s.s. differences in favour of aVNS compared to sham treatment

Population Two: Chronic pain

Population 2: patients with chronic pain

The quality of the evidence of the six RCTs ranged from low to high, with most of the studies rated as having a moderate to high risk of bias.

Clinically and statistically significant improvements in pain and symptom severity ($p \leq 0.001$ for both) were observed in youth with pain-related gastrointestinal disorders (aged 11 to 18 years) and adults with constipation-predominant irritable bowel syndrome during a three- to four-week regimen of percutaneous or transcutaneous aVNS, compared with sham treatment (both in addition to standard care). The reductions in pain scores were sustained in the 11- to 18-year-old patients for a median 9.2 weeks after treatment cessation.

abdominal pain: s.s. improvement in pain and symptom severity in children, adolescents and adults

In one RCT, transcutaneous aVNS significantly reduced pain in patients with episodic migraine without aura, compared with sham treatment (p=0.008), but this did not translate into statistically significantly different improvements in quality of life or psychometric measures between the two groups, relative to baseline values, over the four-week course of treatment.

episodic migraine without aura: s.s. pain reduction, no difference in QoL

One RCT found that the addition of transcutaneous aVNS to a conventional regimen of trigger point ischaemic compression and stretching exercises significantly improved pain and grip strength ($p < 0.001$ for both) in patients with myofascial pain syndrome, compared with the conventional care regimen alone. However, this did not result in any statistically significant differences in quality of life between the two treatments.

myofascial pain syndrome: s.s. improvement of pain combining aVNS with conventional treatment, no difference in QoL

Results from one RCT suggested that there was no statistically significant difference between transcutaneous aVNS and sham treatment in reducing pain or symptom severity in patients with chronic fibromyalgia. Similarly, supplementing a home-based exercise program with transcutaneous aVNS for women with chronic fibromyalgia provided no additional benefit over the exercise program alone with respect to pain, symptom severity, quality of life or psychometric measures.

fibromyalgia: no s.s. improvement of pain

Safety

The rates of device-related adverse events in the six RCTs that reported them (four for acute pain and two for chronic pain) were similar between the treatment groups and ranged from 0% to 19%. These minor complications included ear discomfort, tiredness and adhesive allergy.

device-related adverse events: 0 - 19%

Upcoming evidence

12 ongoing RCTs:

1 RCT on acute, postoperative pain and 12 on chronic pain

Twelve ongoing RCTs were identified. One RCT will assess the use of aVNS versus sham treatment for the relief of postoperative pain in 600 patients undergoing arthroplasty. A further six RCTs will examine the use of aVNS to relieve pain in chronic musculoskeletal condition (36 to 148 patients). The other five RCTs will assess the use of aVNS in a variety of pain-related conditions, including radiotherapy-related neuropathic pain, post-stroke complex regional pain syndrome, cyclic vomiting syndrome, chronic pelvic pain and chronic pain related to opioid withdrawal (47 to 116 patients).

Discussion

different conditions, stimulation settings and length of treatment

unclear which different neural trunks in the auricle were stimulated during aVNS

The variation in conditions, stimulation settings and lengths of treatment cycles across the included studies is indicative of the exploratory nature of aVNS in pain control. Although the included studies were restricted to only trials that applied electrodes to areas of the ear innervated by the vagus nerve or specifically mentioned targeting the vagus nerve, three of the four studies on acute pain and one on chronic pain targeted the auricular branches of other nerves as well. In addition, six of the ten included studies used transcutaneous aVNS, which produces a more diffuse stimulation field that may have inadvertently stimulated non-vagal nerves. All of these factors underline the fact that it is not completely clear from the evidence which of several nerve trunks innervating the auricle were being activated during aVNS. Also, the limited understanding of local target engagement and mechanism of action of aVNS means that it is difficult to implement a sham treatment that produces satisfactory perception in the therapeutic group without engaging a therapeutic pathway.

results not transferable to other population groups

While the studies provided evidence that aVNS may be therapeutic for some pain conditions, the results cannot be extrapolated beyond these patient groups. Most of the effects were only observed in a single RCT and require further validation, particularly given the limitations in the evidence base noted above and that the execution of some studies cannot rule out contributions from placebo effects.

aVNS not included in hospital benefit catalogue in Austria

Auricular VNS is currently not included in the hospital benefit catalogue (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence, is not a fully reimbursable service in the Austrian healthcare system.

Conclusion & recommendation

aVNS: safe and effective adjunctive therapy for rebound pain after ACL reconstruction…

The limited evidence indicates that transcutaneous aVNS may be a safe and effective adjunctive treatment for reducing rebound pain after femoral nerve block in patients undergoing anterior cruciate ligament reconstruction. Limited low certainty evidence does not support the use of aVNS for other type of acute postoperative pain.

…and some chronic pain

recommendation: inclusion of aVNS only for selected patients

The limited evidence also suggests that percutaneous aVNS is a safe and effective adjunctive therapy for reducing pain and improving symptoms in pain-related gastrointestinal disorders, particularly irritable bowel syndrome in children and adolescents (aged 11 to 18 years). Lower certainty evidence from one RCT indicated that this may also be true for adults (18 to 75 years of age). Adjunctive transcutaneous aVNS may reduce pain in patients with myofascial pain syndrome or episodic migraine without aura, but the results should be interpreted with caution owing to the lower certainty of evidence for these indications. Based on the available evidence the inclusion of aVNS in the hospital benefit catalogue should therefore be limited to selected patients.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

akute und chronische Schmerzen

Schmerzen sind eine der Hauptursachen für die Inanspruchnahme von medizinischer Hilfe. Es kann zwischen akutem (plötzlich, kurz auftretendem) und chronischem (langanhaltendem) Schmerz unterschieden werden. Chronische Schmerzen sind oft sekundär und sind damit ein Symptom einer anderen Erkrankung. Daneben gibt es auch chronische primäre Schmerzen, wie Fibromyalgie und das Reizdarmsyndrom, die eine eigenständige Krankheit darstellen.

50% der Patient*innen (Pat.) erhalten nach Operationen (OPs) keine angemessene Schmerzbehandlung

Weniger als 50 % der Patient*innen erhalten nach einer Operation eine angemessene postoperative Schmerzbehandlung. Dabei haben unzureichend behandelte akute, postoperative Schmerzen negative Auswirkungen auf die Lebensqualität und die funktionelle Erholung. Außerdem erhöhen sie das Risiko für postoperative Komplikationen und chronische postoperative Schmerzen, welche bei bis zu 10 % der Patient*innen nach einem chirurgischen Eingriff auftreten.

2019: 56% der Österreicher*innen (> 15 Jahre) litten innerhalb der vorangegangenen vier Wochen an Schmerzen

chronische Schmerzen beeinträchtigen Funktionsfähigkeit und Wohlbefinden

Die Prävalenz von chronischen Schmerzen ist in den verschiedenen Bevölkerungsgruppen auffallend einheitlich und liegt zwischen 11 % und 14 %. Kreuz-, Kopf- und Bauchschmerzen sind die am häufigsten berichteten Schmerzzustände bei Kindern und Jugendlichen, während Erkrankungen des Bewegungsapparats die häufigsten Ursachen für Schmerzen bei älteren Menschen sind. Im Jahr 2019 gaben in Österreich rund 4,1 Millionen (56 %) Jugendliche und Erwachsene (>15 Jahre) an, innerhalb der letzten vier Wochen unter körperlichen Schmerzen gelitten zu haben. Die Häufigkeit von körperlichen Schmerzen steigt mit zunehmendem Alter deutlich an, von 42 % bei den 15- bis 29-Jährigen auf 74 % bei den über 75-Jährigen. Chronische Schmerzen beeinträchtigen die Funktionsfähigkeit und das Wohlbefinden erheblich. Sie führen zu einem schlechten Allgemeinzustand, zu Behinderungen, Depressionen, sozialem Rückzug, zu einer geringeren Lebenserwartung und zu einem erhöhten Risiko für andere Komorbiditäten.

Beschreibung der Technologie

aurikuläre Vagusnerv-stimulation (aVNS): Schmerzbeeinflussung durch schwache elektrische Stromimpulse

Gerät mit zwei Hauptkomponenten: 1 tragbarer Stimulator & Elektroden die mit dem Stimulator über dünne Kabel verbunden sind

Unter Neuromodulation versteht man die Beeinflussung der Nervensystem-aktivität durch elektrische Stimulationen und pharmazeutische Wirkstoffe. Die Modulation soll einen therapeutischen Nutzen, z. B. eine Schmerzlinderung, erzielen. Eine Möglichkeit der Neuromodulation ist die aurikuläre Vagus-nervstimulation (aVNS). aVNS-Geräte bestehen aus zwei Hauptkomponenten: einer tragbaren Stimulationseinheit oder einem Impulsgenerator und einer Oberflächen- oder Nadelelektrode, die an der Außenfläche des Ohrs angebracht und über einen dünnen Draht mit dem Stimulator verbunden wird. Das Gerät gibt schwache elektrische Stromimpulse ab, die über das Kabel entlang des Vagusnervs an das Gehirn übertragen werden, um so den Schmerz zu beeinflussen. Ein üblicher täglicher Behandlungszyklus umfasst drei bis vier Stimulationssitzungen mit einer Gesamtdauer von vier bis fünf Stunden, wobei jede Sitzung mindestens eine Stunde dauert. Die Gesamtlänge einer VNS-Behandlung variiert je nach Indikation.

Methoden

Projektziel: Wirksamkeit & Sicherheit von aVNS bei Schmerzen

Ziel dieses Berichts war es, die Sicherheit und Wirksamkeit von aVNS im Vergleich zu einer Scheinbehandlung oder einer Standardbehandlung bei den folgenden zwei Patientengruppen zu bewerten:

- Population 1: Patient*innen mit **akuten postoperativen Schmerzen;**
- Population 2: Patient*innen mit **chronischen Schmerzen.**

systematische Suche in 4 Datenbanken

Die systematische Literatursuche wurde am 7. Dezember 2022 in vier medizinischen Datenbanken durchgeführt. Die folgenden Datenbanken wurden durchsucht: Medline, Embase, The Cochrane Library und die INAHTA Database. Es wurden nur randomisierte kontrollierte Studien in die Evidenzsynthese eingeschlossen.

Studienauswahl, Extraktion & Qualitätsbeurteilung: von 2 Forscherinnen durchgeführt

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden unabhängig voneinander von zwei Autorinnen (AS, VH, RAF) durchgeführt. Die Bewertung der Qualität der eingeschlossenen Studien erfolgte mit dem Cochrane Risk of Bias Tool v.2 und die Qualität der Evidenz wurde nach dem GRADE-Bewertungsschema (GRADE - Grading of Recommendations, Assessment, Development and Evaluations) eingestuft.

Klinische Wirksamkeit

Wirksamkeit: entscheidungsrelevante Endpunkte

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert:

- **akute ostoperative Schmerzen:** Schmerzen, Analgetikaverbrauch und Verwendung von Notfallmedikamenten;
- **chronische Schmerzen:** Schmerzen, körperliche Funktionsfähigkeit und Schweregrad der Symptome.

Sicherheit

Sicherheit: entscheidungsrelevante Endpunkte

Der folgende Endpunkt wurde für die Bewertung der Sicherheit als entscheidend definiert: gerätebezogene unerwünschte Ereignisse (einschließlich Verträglichkeit und Sicherheit).

Ergebnisse

Verfügbare Evidenz

Insgesamt wurden zehn RCTs identifiziert, die die vordefinierten Einschlusskriterien erfüllten:

10 RCTs: 4 für Population 1 6 für Population 2

- **akuter postoperativer Schmerz:** 4 RCTs zu laparoskopischer oder offener Dünn- oder Dickdarmresektion mit oder ohne Stoma, geplanter Kaiserschnittentbindung, elektiver Entfernung eines Weisheitszahns im Unterkiefer und Rekonstruktion des vorderen Kreuzbandes,
- **chronischer Schmerz:** 6 RCTs zu abdominalen Schmerzen (2 RCTs), Fibromyalgie (2 RCTs), episodischer Migräne ohne Aura (1 RCT), myofaszialem Schmerzsyndrom (1 RCT)

Klinische Wirksamkeit

Patient*innen mit akuten postoperativen Schmerzen

Pat. mit akuten postoperativen Schmerzen

Die aktiven und Scheinbehandlungen wurden in allen vier RCTs zusätzlich zur jeweiligen Standardbehandlung eingesetzt. Die RCTs wurden mit einem niedrigen bis hohen Verzerrungsrisiko bewertet, wobei lediglich eine Studie mit einem geringen Risiko für Verzerrungen bewertet wurde.

niedriges bis hohes Verzerrungsrisiko

Die Kombination von perkutaner aVNS mit der Standardbehandlung zeigte bei den Schmerzwerten, dem Analgetikaverbrauch oder dem Einsatze von Notfallmedikamenten nach einem geplanten Kaiserschnitt oder einer chirurgischen Weisheitszahnextraktion keine statistisch signifikanten Unterschiede im Vergleich zu einer Scheinbehandlung in Kombination mit der Standardversorgung oder der Standardversorgung allein. Ähnliche Ergebnisse wurden in zwei weiteren RCTs beobachtet, die perkutane aVNS mit Ohrakupunktur über einen zwei- bis fünftägigen Behandlungszyklus bei Patient*innen nach einer größeren kolorektalen Operation oder einer chirurgischen Weisheitszahnentfernung verglichen. Im Rahmen einer dieser Studien zeigten sich zusätzlich keine Unterschiede zwischen aktiver Neurostimulation und Ohrakupunktur beim Auftreten von postoperativer Übelkeit und Erbrechen, bei der Dauer des Krankenhausaufenthalts und bei den 30-Tage-Wiederaufnahmeraten.

3 RCTs mit keinen statistisch signifikanten (s.s.) Unterschieden zwischen den Behandlungen bei geplantem Kaiserschnitt, chirurgischer Weisheitszahnentfernung oder kolorektalen Operationen

In einem RCT wurden die Auswirkungen der transkutanen aVNS auf die Linderung von Rebound-Schmerzen nach einer femoralen Nervenblockade bei Patient*innen untersucht, die sich einer Rekonstruktion des vorderen Kreuzbandes unterzogen. Bei den VNS-Patient*innen traten Rebound-Schmerzen in den ersten zwölf Stunden seltener auf (18 % vs. 41 %; p=0,03) und hielten kürzer an (p=0,002). Auch der Analgetikaverbrauch (p=0.02) und die Verwendung von Notfallmedikamenten (p=0.004), sowie Schlafstörungen (p=0.03) in den ersten 12 Stunden nach der Operation unterschieden sich signifikant zugunsten der aVNS-Gruppe.

1 RCT mit s. s. Verbesserung des Rebound-Schmerzes bei Rekonstruktion des vorderen Kreuzbandes

Patient*innen mit chronischen Schmerzen

Pat. mit chronischen Schmerzen

Die Qualität der Evidenz der sechs RCTs reichte von niedrig bis hoch, wobei die meisten Studien mit einem mäßigen bis hohen Verzerrungsrisiko bewertet wurden.

niedriges bis hohes Verzerrungsrisiko

Statistisch und klinisch signifikante Verbesserungen der Schmerzwerte und der Symptomschwere (p≤0,001 für beide) wurden in jeweils einem RCT bei Jugendlichen mit schmerzbedingten gastrointestinalen Beschwerden (im Alter von 11 bis 18 Jahren) und Erwachsenen mit verstopfungsbedingtem Reizdarmsyndrom während einer drei- bis vierwöchigen Behandlung mit perkutaner oder transkutaner aVNS im Vergleich zu einer Scheinbehandlung (beide zusätzlich zur Standardbehandlung) beobachtet. Die Verringerung der Schmerzwerte hielt bei den 11- bis 18-jährigen Patienten im Median für 9,2 Wochen nach Beendigung der Behandlung an.

2 RCTs mit s.s. Verbesserungen von Schmerzen und Symptomschwere bei Kindern, Jugendlichen und Erwachsenen mit gastrointestinalen Symptomen

In einem RCT führte transkutane aVNS bei Patient*innen mit episodischer Migräne ohne Aura im Vergleich zu einer Scheinbehandlung zu einer statistisch signifikanten Schmerzreduktion (p=0.008). Bei der Lebensqualität und den psychometrischen Messwerten konnten während der vierwöchigen Behandlung keine signifikanten Unterschiede zwischen den beiden Gruppen im Vergleich zum Ausgangswert festgestellt werden.

1 RCT mit s.s. Schmerzreduktion bei episodischer Migräne, kein Unterschied bei LQ

1 RCT mit s.s. Verbesserung von Schmerzen bei Pat. mit myofaszialem Schmerzsyndrom, kein Unterschied bei LQ

Ein RCT zeigte, dass bei Patient*innen mit myofaszialem Schmerzsyndrom die Kombination von transkutaner aVNS mit einer konventionellen Behandlung (ischämische Kompression der Triggerpunkte und Dehnungsübungen) im Vergleich zur konventionellen Behandlung allein zu einer signifikanten Verbesserung der Schmerzen ($p<0.001$) und der Griffkraft ($p<0.001$) führte. Die Lebensqualität unterschied sich jedoch nicht statistisch signifikant zwischen den beiden Gruppen.

2 RCTs: keine s.s. Unterschiede bei Fibromyalgie

Die Ergebnisse aus einem RCT konnten keine statistisch signifikanten Unterschiede zwischen transkutaner aVNS und einer Scheinbehandlung bei Patient*innen mit chronischer Fibromyalgie in Bezug auf die Verringerung der Schmerzen oder der Symptomschwere feststellen. Auch die Kombination eines häuslichen Trainingsprogramms mit transkutaner aVNS bei Frauen mit chronischer Fibromyalgie zeigte keine statistisch signifikanten Unterschiede gegenüber dem Trainingsprogramm bei Schmerzen, Symptomschwere, Lebensqualität oder psychometrischen Messwerten.

Sicherheit

gerätebezogene unerwünschte Ereignisse: 0 – 19 %

Die Häufigkeit gerätebezogener unerwünschter Ereignisse, welche von sechs RCTs berichtet wurden (vier für akute Schmerzen und zwei für chronische Schmerzen), war zwischen den Behandlungsgruppen ähnlich und reichte von 0 % bis 19 %. Zu diesen geringfügigen berichteten Komplikationen gehörten Ohrenbeschwerden, Müdigkeit und Klebstoffallergie.

Laufende Studien

12 laufende RCTs:

1 RCT zu akuten, postoperativen Schmerz und 12 zu chronischen Schmerz

Zwölf laufende RCTs wurden identifiziert. Ein RCT untersucht den Einsatz von aVNS im Vergleich zu einer Scheinbehandlung zur Linderung von postoperativen Schmerzen nach einer Endoprothese bei 600 Patient*innen. Von den anderen elf RCTs untersuchen sechs den Einsatz von aVNS zur Schmerzlinderung bei chronischen muskuloskelettalen Erkrankungen (36 – 148 Patient*innen) und bei fünf RCTs wird der Einsatz von aVNS bei einer Reihe von Schmerzzuständen (47 bis 116 Patient*innen) untersucht.

Diskussion

unterschiedliche Bedingungen, Stimulationseinstellungen und Länge der Behandlung

teilweise unklar welche der verschiedenen Nevenstränge in der Ohrmuschel stimuliert wurden

Die Unterschiede bei den Bedingungen, Stimulationseinstellungen und der Länge der Behandlungszyklen in den eingeschlossenen Studien weisen auf den experimentellen Charakter der aVNS im Bereich der Schmerzbehandlung hin. Obwohl sich die eingeschlossenen RCTs auf Studien beschränkten, die Elektroden in Bereichen des Ohrs anbrachten, die vom Vagusnerv innerviert werden, oder die speziell auf den Vagusnerv abzielten, haben drei der vier Studien zu akuten Schmerzen und eine Studie zu chronischen Schmerzen auch die aurikulären Äste anderer Nerven stimuliert. Außerdem wurde in sechs der zehn eingeschlossenen Studien die transkutane aVNS verwendet, die ein diffuseres Stimulationsfeld erzeugt, das unbeabsichtigt auch andere Nerven als den Vagusnerv stimuliert haben könnte. All diese Faktoren unterstreichen die Tatsache, dass aus den vorliegenden Daten nicht eindeutig hervorgeht, welche der verschiedenen Nervenstämme, die die Ohrmuschel innervieren, während der aVNS aktiviert wurden. Außerdem ist es aufgrund des begrenzten Verständnisses des lokalen Ziels und des Wirkmechanismus der aVNS schwierig, eine Scheinbehandlung durchzuführen, die in der therapeutischen Gruppe eine zufriedenstellende Wahrnehmung erzeugt, ohne einen therapeutischen Signalweg zu aktivieren.

Die Studien lieferten zwar Hinweise, dass aVNS bei einigen Schmerzzuständen im Vergleich zu einer Scheinbehandlung oder Standardbehandlung wirksamer sein kann. Es ist fraglich, ob die Anhaltspunkte für einen Zusatznutzen auch auf andere Populationen übertragbar sind.

Ergebnisse nicht auf andere Personengruppen übertragbar

Derzeit ist aVNS nicht im Leistungskatalog der leistungsorientierten Krankenanstaltenfinanzierung (LKF) enthalten und somit keine voll erstattungsfähige Leistung im österreichischen Gesundheitssystem.

aVNS derzeit nicht im Leistungskatalog in Österreich

Schlussfolgerung und Emfpehlung

Die verfügbare limitierte Evidenz deutet darauf hin, dass die transkutane aVNS eine sichere und wirksame Zusatzbehandlung zur Verringerung von Rebound-Schmerzen nach einer Blockade des Nervus femoralis bei Patient*innen sein kann, die sich einer Rekonstruktion des vorderen Kreuzbandes unterziehen. Die limitierte Evidenz mit geringer Vertrauenswürdigkeit sprechen nicht für den Einsatz der aVNS bei anderen Arten von akuten postoperativen Schmerzen.

postoperativer Schmerz: sichere und wirksame Zusatztherapie bei Rebound-Schmerzen nach ACL-Rekonstruktion

Die verfügbare Evidenz deutet auch darauf hin, dass die perkutane aVNS eine sichere und wirksame Zusatztherapie zur Schmerzlinderung und Verbesserung der Symptome bei schmerzbedingten gastrointestinalen Erkrankungen, insbesondere beim Reizdarmsyndrom bei Kindern und Jugendlichen (11 – 18 Jahre), ist. Hinweise deuten darauf hin, dass dies auch auf Erwachsene (18 bis 17 Jahre) zutreffen könnte. Die transkutane aVNS kann bei Patient*innen mit myofaszialem Schmerzsyndrom oder episodischer Migräne ohne Aura zu einer Schmerzlinderung führen, doch sollten die Ergebnisse aufgrund der geringeren Beweissicherheit für diese Indikationen mit Vorsicht interpretiert werden. Basierend auf der verfügbaren Evidenz sollte die Aufnahme von aVNS in den Krankenhausleistungskatalog daher auf ausgewählte Patient*innen beschränkt werden.

chronischer Schmerz: sichere und wirksame Zusatztherapie bei ausgewählten Patient*innen und Indikationen

Empfehlung: Aufnahme nur für ausgewählte Patient*innen

1 Background

1.1 Overview of the disease, health condition and target population

Schmerz = Hauptgrund für Inanspruchnahme von medizinischer Hilfe

Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage. It is the main reason people seek medical care [1]. There are three main types of physical pain [2-5].

nozizeptiver Schmerz: Schädigung von nicht-Nervengewebe, verschwindet (normalerweise) nach Heilung wieder

- *Nociceptive:* This is the most common type of pain. It results from damage to non-neural tissue and tends to go away once the affected body part heals. Nociceptive pain is further categorised as either somatic (originating in peripheral tissues such as skin, muscle and bone) or visceral (occurring in organs of the abdomen and chest). This type of pain is associated with trauma, such as fractures, burns, muscle tears and sprains; muscle spasms; degenerative changes resulting from normal wear and tear, such as primary osteoarthritis; and visceral pathologies such as ulcers, renal stones and pancreatitis.

neuropathischer Schmerz: Krankheiten oder Verletzungen, die das somatosensorische Nervensystem (NS) betreffen

- *Neuropathic:* This type of pain arises from diseases or injuries affecting the somatosensory nervous system. Conditions associated with neuropathic pain include nerve or nerve root compression (e.g., radiculopathy, carpal tunnel syndrome and trigeminal neuralgia); exposure to toxins (e.g., chemotherapy); metabolic diseases such as diabetes; ischaemia (e.g., peripheral vascular disease and diabetic neuropathy); trauma (e.g., postsurgical pain); infections (e.g., shingles and human immunodeficiency viruses); and inflammation (e.g., inflammatory demyelinating polyradiculoneuropathy).

noziplastischer Schmerz: unabhängig von Gewebs- oder Nervenschäden

- *Nociplastic:* This pain is caused by the activation of peripheral pain-related sensory pathways in the absence of actual tissue or nerve damage. Nociplastic pain can occur in isolation or in combination with nociceptive or neuropathic pain. It is often associated with bladder pain syndrome, fibromyalgia, chronic pelvic pain, irritable bowel syndrome, temporomandibular disorder, some types of tension-type headaches and non-specific back pain.

akuter Schmerz: plötzliches Auftreten, kurze Dauer und eine offensichtliche Ursache

chronischer Schmerz: langanhaltend, über die erwartete Heilungszeit hinaus

Pain can be further categorised as acute or chronic.[1], Acute pain is a psycho-physiological response to tissue trauma and re-lated inflammatory processes and has a valuable survival function. It has a sudden onset, short duration and an obvious cause [3]. In con-trast, chronic pain is a maladaptive pain that persists beyond the ex-pected healing time of injured tissues (three months according to In-ternational Classification of Diseases [6]) [2]. Chronic secondary pain is usually a symptom of another condition, whereas chronic primary pain is a disease unto itself. Examples of chronic primary pain conditions include fibromyalgia and complex regional pain syndromes, irri-table bowel syndrome and nonspecific low back pain [3]. The relevant International Classification of Diseases (ICD)-11 codes for the various acute and chronic pain conditions are listed in Table 1 1.

[1] **A0002** What is the disease or health condition in the scope of this assessment?

Table 1-1: Relevant ICD-11 codes for pain

Pain type	ICD-11 code
Abdominal or pelvic pain	MD81
Migraine	8A80
Low back pain	ME84.2
Symptom or complaint of the back, unspecified	ME86.2Z
Chronic pain	**MG30**
Chronic primary pain	MG30.0
Chronic cancer related pain	MG30.1
Chronic postsurgical or post-traumatic pain	MG30.2
Chronic secondary musculoskeletal pain	MG30.3
Chronic secondary visceral pain	MG30.4
Chronic neuropathic pain	MG30.5
Chronic secondary headache or orofacial pain	MG30.6
Other specified chronic pain	MG30.Y
Chronic pain, unspecified	MG30.Z

Source: International Classification of Diseases 11th Revision [7]

chronische Schmerzen: körperliche, psychologische und soziale Risikofaktoren

There are many physical, psychological and social risk factors associated with developing chronic pain. Predisposing characteristics fall into various categories, including demographic (e.g., female sex, older age and adverse socioeconomic conditions); lifestyle and behaviour (e.g, smoking, obesity and lack of physical activity); and clinical (e.g., another site of acute or chronic pain within the body or the presence of comorbid physical and mental chronic diseases) [2, 8].[2]

2 verschiedene Populationen für Bewertungen

Therefore, there are two distinct populations for this assessment: patients with acute postoperative pain and those with chronic pain of at least three months' duration.[3]

1.1.1 Epidemiology[4]

Acute postoperative pain

inadäquate Schmerztherapie nach Operation: ↑ Risiko für postoperative (postop.) Komplikationen & chronische, postop. Schmerzen

10 % der Pat. leiden an chronischen, postop. Schmerz

Inadequately controlled postoperative pain not only negatively affects quality of life and functional recovery, it also increases the risk of post-surgical complications and of developing chronic postsurgical pain (CPSP), which is pain that persists for at least three months after a surgical procedure [9, 10]. CPSP affects up to 10% of patients and is particularly common after amputations (50% to 85%), thoracotomies (5% to 65%), cardiac surgery (30% to 55%) and breast surgery (20% to 50%) [11]. However, it also occurs after minor procedures such as hernia repair [9]. In Austria, 1,161,787 surgeries were performed in 2021, an increase of almost 6% compared with 2020 [12]. CPSP is more common among women and younger patients than other individuals [13]. Other risk factors for developing CPSP include anxiety, severe acute postoperative pain, early postoperative hyperalgesia, surgical

[2] **A0003** What are the known risk factors for the disease or health condition?

[3] **A0007** What is the target population in this assessment?

[4] **A0023** How many people belong to the target population?

procedures lasting longer than three hours and infection [9, 11, 14, 15]. Inadequate preventive analgesia may also contribute to the development of CPSP [9].[2,5] Evidence suggests that less than 50% of patients undergoing surgery receive adequate postoperative pain relief [16].

Chronic pain

11 – 14 % der Bevölkerung leidet an chronischen Schmerzen

The prevalence of chronic widespread pain is remarkably consistent among populations, ranging from 11% to 14% [17]. Low back pain, headache and abdominal pain are the most commonly reported pain conditions among children and adolescents [17]. Self-reported chronic pain in at least two sites (headache, stomach or back ache) is reported by approximately 21% of young people, while chronic pain affects up to 30% of those aged 18 to 39 years [8, 18]. Systematic reviews of epidemiological studies report that the median one-month prevalence of chronic back pain, headache and abdominal pain among children and adolescents is 21%, 48% and 12%, respectively [17].

muskuloskelettale Erkrankungen = häufigster Grund für Schmerzen im Alter

Musculoskeletal disorders are one of the most common causes of pain in older individuals. The prevalence of chronic low back pain in the general population in Europe ranges from 6% to 11% (median 9%) [19, 20]. The median prevalence of shoulder pain is 16% [21], and one in four people over the age of 55 years experiences a persistent episode of knee pain over a one-year period [22].

2019: 56 % der Österreicher*innen berichteten über Schmerzen innerhalb der vorangegangenen 14 Tage

In 2019, approximately 4.1 million Austrians (56%) older than 15 years reported experiencing some degree of physical pain in the previous four weeks, with higher rates occurring among women than men (60% versus 52%) [12]. In the same year, the twelve-month prevalence rates for pain-related conditions were as follows: chronic back ailments (26%); neck disorders or other chronic complaints of the cervical spine (20%); osteoarthritis (14%); chronic headache (8%); and chronic inflammatory bowel disease (3%). The frequency of physical pain increased considerably with advancing age, rising from 42% among 15- to 29-year-olds to 61% of 60- to 74-year-olds and 74% among those older than 75 years [12]. Older people were also more likely to experience severe or very severe pain than younger individuals (24% versus 13%) [23].

1.1.2 Burden of disease

chronischer Schmerz: negative Auswirkungen auf Wohlbefinden und das soziale Leben

Chronic pain interferes considerably with functioning and wellbeing, resulting in poor general health, disability, depression and social withdrawal, and an increased risk of developing further comorbidities [9, 17]. Chronic pain also negatively affects relationships, self-esteem and overall perceptions of general health, and is associated with higher divorce and suicide rates, an increased risk of substance abuse and a lower life expectancy [2].[5]

durch Schmerz gekennzeichnete Erkrankungen: hohe Anzahl an verlorenen Lebensjahren aufgrund von Behinderung

Globally, conditions characterised or defined by the presence of pain (such as low back pain, neck pain, other musculoskeletal disorders, migraine and falls) accounted for five of the top ten conditions responsible for the most years lost due to disability [24]. The corresponding disability-adjusted life years (DALYs) were 83 million for low back pain, 24 million each for neck pain and migraine/headache, 28 million for other musculoskeletal disorders, 19 million for falls and 17 million for osteoarthritis [25].[6]

---

[5] **A0004** What is the natural course of the disease or health condition?

[6] **A0005** What is the burden of disease for the patients with the disease or health condition?

Behandlung von Schmerzen: verschiedene Dienstleistungen involviert

hohe direkte und …

The management of pain requires an array of services, including physical therapy (17%) and inpatient care (17%), pharmacy (13%) and primary care (13%) [17]. A study in Europe of patients with chronic pain found that at least 93% had visited their physician in the previous six months, compared with 84% of the general adult population [20]. In Austria, patients with chronic pain visit their primary care provider an average of eight times per year. It takes an average of 1.7 years for a patient in Austria with chronic pain to be correctly diagnosed, and a further 1.9 years to receive appropriate treatment [23, 26]. Consequently, patients with pain conditions consume nearly twice as much healthcare resources as the general population [17].[7]

… indirekte Kosten für das Gesundheitssystem und die Gesellschaft

In addition to these direct costs, there are considerable indirect costs arising from reduced earning capacity, inability to work and early retirement [26]. It has been estimated that individuals with moderate to severe chronic pain lose an average of eight days of work every six months, with 22% losing at least ten workdays [20]. With the aging workforce in many countries, the social and economic impact of older workers having to retire due to painful health conditions is likely to be considerable [17]. In Austria, diseases of the musculoskeletal system are responsible for the loss of 660,000 annual workdays, corresponding to half of the days lost per annum [23].

1.2 Current clinical practice[8]

Leitlinien empfehlen interdisziplinäre Behandlung

Since pain is a consequence of various biological, psychological, and social factors, guidelines generally recommend interdisciplinary treatment, ideally within a shared-decision model that encompasses a personalised approach [2, 27].

1.2.1 Guidelines for acute pain

Leitlinie akuter Schmerz:

ASRA and ASA:

regionale analgetische Techniken in Kombination mit systemischen Medikamenten (z.B. Opioide) und nicht-pharmakologischen Interventionen (z.B. TENS)

A guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine and the American Society of Anesthesiologists recommends using a variety of local anaesthetic-based regional analgesic techniques, in combination with systemic drugs and nonpharmacological interventions, that target different mechanisms of action in the peripheral and central nervous system (strong recommendation, high-quality evidence) [16]. The components of this multimodal regimen vary depending on the patient, setting and surgical procedure. Preferred pharmacological interventions include oral opioids (strong recommendation, moderate quality evidence), acetaminophen and/or nonsteroidal anti-inflammatory drugs (strong recommendation, high-quality evidence) and gabapentin or pregabalin (strong recommendation, moderate-quality evidence). Recommended adjunctive treatments include cognitive behavioural modalities (weak recommendation, moderate-quality evidence) and transcutaneous electrical nerve stimulation (TENS) (weak recommendation, moderate-quality evidence), which delivers alternating current via cutaneous electrodes positioned near the painful area and is different from the more targeted aVNS. Although opioids are the reference standard for treating acute postoperative pain, this is tempered by the fact that around 6% of individuals who receive opioids after surgery end up on chronic opioid therapy [2, 27]. In addition, the side effects of opioids

[7] **A0006** What are the consequences of the disease or health condition for the society?

[8] **A0025** How is the disease or health condition currently managed according to published guidelines and in practice?

include excess sedation, respiratory depression, opioid-induced constipation and postoperative nausea and vomiting. Thus, the choice of treatment regimen must take into account the side effect profile for each analgesic medication or technique used and the patient's risk factors for adverse events.

AWMF-S3-Leitlinie:

The German AWMF S3-guideline recommends a similar pharmacological strategy for the treatment of acute perioperative and post-traumatic pain, as well as the following adjunctive therapies [28].

Psychologische/ psychotherapeutische Maßnahmen,

- Psychological/psychotherapeutic measures should be integrated into the perioperative/post-traumatic pain management on an individualized and age-group-specific basis (recommendation grade A, level of evidence 1)
- Physiotherapeutic measures should be integrated into post-operative/ post-traumatic pain management (recommendation grade A, level of evidence 1)

Kältetherapie,

- Postoperative cold therapy should be recommended after some surgical orthopaedic procedures (recommendation grade B, level of evidence 1).

TENS,

- The additional use of TENS should be used for certain indications (recommendation grade B, level of evidence 1).

Akupunktur

- Acupuncture can be used as an adjuvant measure for certain indications (recommendation grade C, level of evidence -).

1.2.2 Guidelines for chronic pain

Leitlinien chronische Schmerzen:

NICE: primärer Schmerz: multimodaler Ansatz

versch. krankheits-spezifische Leitlinien zu sekundärem Schmerz

For chronic primary pain, guidelines from the National Institute of Health and Care Excellence in the United Kingdom recommend a multimodal approach that includes physical activity and supervised group exercise programs, psychological therapy (e.g., commitment therapy or cognitive behavioural therapy), acupuncture and antidepressants [29]. For chronic secondary pain, there are various guidelines for managing the underlying conditions (e.g., headache, irritable bowel syndrome, low back pain and sciatica, neuropathic pain, osteoarthritis, rheumatoid arthritis and spondylarthritis), each of which provides condition-specific recommendations for relieving pain [30]. If the pain associated with these conditions is considered out of proportion to the underlying disease, then the pain is managed using the more general recommendations for chronic primary pain above.[9]

AWMF S1-Leitlinie: multimodaler, strukturierter Ansatz

The German AWMF S1-guideline (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.) also recommends a multimodal, structured approach for managing chronic non-cancer related pain. This includes patient education, interventions for improving function and mood (e.g., physiotherapy, exercise, relaxation, psychotherapy and antidepressants) and self-management, such as participation in group physical or social activity programs, self-help groups and rehabilitation programs [31].

[9] **A0018** What are the other typical or common alternatives to the current technology?

1.3 Features of the intervention

Vagusnerv (VN) = längster Hirnnerv

The cranial nerves are a set of twelve paired nerves that have motor and/or sensory functions and connect the brain with the head, neck and torso. The longest of these is the vagus nerve (cranial nerve X), which extends from the thoracic and visceral abdominal organs up to the higher cerebral centres of the locus ceruleus, dorsal motor nucleus of the vagus, medulla, amygdala, hypothalamus, parabrachial nucleus and thalamus [32-34]. The afferent fibres, which comprise 80% of the nerve, carry sensory information from the head, neck, thorax and abdomen to the brain, while the efferent fibres (constituting 20% of the nerve) carry motor information to the pharynx, larynx, trachea, heart, aorta, lungs and gastrointestinal tract (oesophagus, stomach, liver, pancreas and spleen). Consequently, the vagus nerve regulates a variety of functions within the autonomic, cardiovascular, respiratory, gastrointestinal, immune and endocrine systems, including digestion, heart rate, blood pressure, vascular resistance, airway diameter, respiration and reflex actions such as coughing, sneezing, swallowing and vomiting. The vagus nerve also appears to have a role in regulating the neuro-endocrine-immune axis, mood, pain and memory [33-35].

VN reguliert eine Vielzahl von Funktionen im Körper (z.B. Verdauung, Herzfrequenz und Blutdruck)

VN beeinflusst Schmerz durch Hemmung und Aktivierung von Mechanismen die, die Schmerzwahrnehmung beeinflussen

The vagus nerve is thought to modulate pain through its ability to inhibit inflammation, oxidative stress and sympathetic activity and to activate brain regions that influence pain perception, such as the thalamus, hypothalamus, left prefrontal cortex and the periaqueductal gray [32, 36].[10] Consequently, the vagus nerve has become an attractive target for addressing various diseases and pain-related conditions through neuromodulation, which is the manipulation of nervous system activity using either electrical or pharmaceutical agents to achieve a therapeutic benefit, such as pain relief [37, 38].

elektrische Vagusnervstimulation (VNS) seit 1994 in Europa bei Epilepsie zugelassen

invasive VNS hat mehrere Nachteile im Zusammenhang mit der Drahtimplantation/-explantation und der Stimulation

Electrical vagus nerve stimulation (VNS) was approved in Europe as an adjunctive treatment for epilepsy in 1994 and for refractory depression in 2001. VNS has also been trialled as a potential treatment for other diseases, such as rheumatoid arthritis and heart failure [39, 40]. Invasive VNS involves wrapping a wire around the left vagus nerve in the neck and connecting it to an electrical nerve stimulator (or pulse generator) that is implanted under the skin on the left side of the chest. The device emits low-level pulses of electrical current that are transmitted via the wire along the vagus nerve to the brain. Despite its effectiveness, the mechanism of action of VNS is still not completely understood. The side effects related to wire implantation (infection and vocal cord paresis) and stimulation (hoarseness, voice changes and cough) have limited the intervention's application to patients who are resistant to conventional therapeutic strategies [41, 42]. An additional problem with invasive VNS is that the electrode wires are hard to remove without damaging the vagus nerve [43].

Alternative zur invasiven VNS = aurikuläre VNS (aVNS)

VN wird über Nervenbahnen in Ohrmuschel stimuliert

To avoid these difficulties, several devices have been designed to electrically stimulate branches of the vagus nerve located in the ear (auricular branch) or neck (cervical branch) either percutaneously (using a needle electrode) or transcutaneously (using a non-invasive surface electrode attached to the skin) [37-39, 44, 45].[11] Anatomical studies of the ear suggest that afferent vagus nerve distributions are located at the inner side of the tragus, the concha and

[10] **A0009** What aspects of the consequences/burden of disease are targeted by the technology?

[11] **B0002** What is the claimed benefit of the technology in relation to the comparators?

the cymba concha [46, 47]. However, the ear also contains endings of non-vagal cervical and cranial nerves such as the great auricular nerve in the ear lobe, the auriculotemporal nerve (a branch of the trigeminal nerve) located in the spine of the helix and the lesser occipital nerve in the upper third of the medial surface of the auricle [35]. The cymba concha is the only region of the ear exclusively innervated by the auricular branch of the vagus nerve [48].

Geräte bestehen aus zwei Hauptkomponenten: 1 tragbarer Stimulator & Elektroden die mit dem Stimulator über dünne Kabel verbunden sind

zwei Arten: transkutane aVNS und perkutane aVNS

Auricular VNS (aVNS) devices comprise two main components: the portable stimulation unit or pulse generator, which is roughly the size of a cell phone and can be controlled by the patient, and an ear electrode that is connected to the stimulator via a thin wire.[12] Smaller stimulators are also available that are the size of a hearing aid and can be affixed to the skin behind the ear. The aVNS electrodes are usually placed on the left ear but may be applied to both ears to boost the stimulation effect [37, 49]. The stimulation current is adjusted until a slight tingling or pulsating sensation is perceived at the stimulation site. Stimulation regimens vary, but a typical daily treatment cycle encompasses three to four stimulation sessions for a total of four to five hours, with each session lasting at least one hour. The total length of aVNS treatment varies depending on the indication. Transcutaneous devices are equipped with earpieces that can be removed when the device is not in use, whereas percutaneous aVNS devices are usually worn over several days until the treatment cycle is complete [37, 44]. Percutaneous aVNS provides a more precise and specific stimulation of the vagus nerve endings than transcutaneous aVNS, which generates a more diffuse stimulation field and, depending on the electrode placement, may inadvertently stimulate non-vagal nerves [37, 45].[13]

aVNS: stimuliert nur die afferenten Endigungen des VN

Since only afferent vagus nerve endings are stimulated with aVNS, the side effects of invasive VNS are avoided [37]. Patients treated with aVNS may experience slight pain, burning, tingling or itching at the stimulation site that dissipates upon electrode removal; local skin irritation (dermatitis); local bleeding (if percutaneous electrodes are used); headache; and dizziness [37, 44]. Contraindications for aVNS therapy include immunocompromise (if semipermanent needle electrodes are used), haemophilia, psoriasis vulgaris at the stimulation site, the presence of a pacemaker or other active implantable devices (which may interference with aVNS) and vagal hyper-sensitivity [37].

versch. Geräte von unterschiedlichen Firmen erhältlich

Several companies have developed specific aVNS devices (see Table 1-2). Stimulation can also be performed using custom-made electrodes attached to a generic transcutaneous electrical nerve stimulator device (e.g., the SNM-FDC01 device, Ningbo Maida Medical Device Inc., Ningbo, China and the TENS 7000, Roscoe Medical, Inc., Ohio, USA) [44].[14]

Administration, investments, personnel and tools required to use the technology and the comparator(s)

einfache Anbringung und Abnahme des Gerätes

Once the provider is trained, the device can be placed in the inpatient (for postoperative pain) or outpatient setting. In the latter case, the device can be removed by the provider in the clinic or by the patient at home. Any medical professional trained in the care of patients with the particular pain condition

[12] **B0009** What supplies are needed to use the technology and the comparator(s)?

[13] **B0001** What is the technology and the comparator(s)?

[14] **B0003** What is the phase of development and implementation of the technology and the comparator(s)?

can administer the device.[12,15] Stimulation parameters vary widely since the optimal electrical current, pulse width, waveform and frequency has yet to be elucidated [44]. Although the typical frequency used ranges between 20 and 30 Hz, frequencies as low as one Hz have also demonstrated a therapeutic effect [44].

Comparators

Schein- oder Standardbehandlung als Kontrolle im Zuge dieses Assessments gewählt

The comparator procedure for aVNS is sham treatment or standard care.[13] Appropriately designed sham treatment encompassed either inactive electrodes placed on the concha or tragus of the ear or active electrodes placed at sites on the ear that are not innervated by the vagus nerve (e.g., the ear lobe or helix), or another part of the body. In the case of percutaneous aVNS, sham treatment with inactive needle electrodes is akin to auricular acupuncture. When a site innervated by the vagus nerve was used, only inactive electrodes were considered an adequate sham treatment since it has been shown that even a one Hz aVNS stimulation can produce a therapeutic effect [50].[15]

Regulatory & reimbursement status

aVNS derzeit nicht im Leistungskatalog in Österreich

- According to the submission materials, the expected annual utilisation of aVNS based on the previous years' experience is 1,000 interventions per year in Austria. The expected annual utilisation of aVNS at the submitting hospital is 200 interventions per year.[16] Currently, aVNS is not included in the hospital catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence, is not a fully reimbursable service in the Austrian healthcare system.[17]

Table 1-2: List of various aVNS devices[18,19]

Device name[a]/ Manufacturer	Electrode Type	CE Mark	US FDA Approval	Class/GMDN code
IB-Stim Auricular Stimulator Bridge™ NeurAxis, Inc., New Hampshire, USA	P	No	Yes Patients aged 11-18 years with functional abdominal pain associated with irritable bowel syndrome (2019)	Class II Product code QHH
NEMOS® t-VNS device tVNS International GmbH (formerly Cerbomed), Erlangen, Germany	T	Yes Epilepsy, depression (2010) Pain (2012)	No	Unclassified

[15] **B0004** Who administers aVNS and the comparators and in what context and level of care are they provided?
[16] **A0011** How much are the technologies utilised?
[17] **A0021** What is the reimbursement status of the aVNS?
[18] **A0020** For which indications has the technology received marketing authorisation or CE marking?
[19] **B0003** What is the phase of development and implementation of the technology and the comparator(s)?

Device name[a]/ Manufacturer	Electrode Type	CE Mark	US FDA Approval	Class/GMDN code
Parasym™ Parasym Ltd, London, United Kingdom	T	Yes (indications unknown)	No	Unclassified
Primary Relief® First Relief® DyAnsys Inc., California, USA	P	No	510(k): K213188 (2022) (Primary Relief) 510(k): K202940 (2020) (First Relief)	Class II Product code NHI (Primary Relief) Product code QHH (First Relief)
P-Stim™ Biegler Medizinelektronik GmbH, Mauerbach, Austria	P	No	510(k): K140788 (2014)	Unclassified Product code BWK
taVNS Stimulator Soterix Medical Inc., New Jersey, USA	T	No	No	Unclassified
Vagustim Vagustim, California, USA	T	No	No	Unclassified
VIVO Aurimod GmbH, Vienna, Austria	P	Yes Pain (2021)	No	Unclassified

[a] *This list is not exhaustive.*

Abbreviations: GMDN – Global Medical Device Nomenclature; P – percutaneous; T- transcutaneous; US FDA – United States Food and Drug Administration

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is electrical aVNS in comparison with sham treatment or standard care more effective or safe with respect to:

- pain, analgesia and rescue medication usage, length of hospitalisation, postoperative nausea and vomiting and adverse events in patients with acute pain?
- pain, physical functioning, symptom severity, use of rescue analgesics and concomitant pain treatments, emotional functioning, participant global ratings improvement, quality of life, pain interference and adverse events in patients with chronic pain?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1: Inclusion criteria2-1.

Table 2-1: Inclusion criteria

Population	**Population One** Patients of any age with acute pain experienced immediately after surgery (up to 7 days) [51] ICD-11 Codes: MG31.2 Acute postoperative pain, not elsewhere classified [7] MeSH and Emtree Terms: ■ Medline: Acute Pain; Pain, Postoperative ■ Embase: Acute pain; Postoperative pain **Population Two** Patients of any age with chronic pain (e.g. abdominal or pelvic pain, back pain or migraine) Chronic pain is defined as pain that persists or recurs for more than 3 months [52] ICD-11 Codes: MD81 Abdominal or pelvic pain; 8A80 Migraine; ME84.2 Low back pain; ME86.2Z Symptom or complaint of the back, unspecified (XT8W chronic); MG30 Chronic pain [7] MeSH and Emtree Terms: ■ MesH: Abdominal Pain; Back Pain; Pelvic Pain; Migraine Disorders; Acute Pain; Chronic Pain; Pain, Postoperative ■ Emtree: Abdominal pain; Pelvic pain; Pelvis pain syndrome; Backache; Low back pain; Chronic pain; Migraine **Rationale** Informed by information provided by the submitting hospital and the International Association for the Study of Pain [52]

Intervention	**Electrical auricular vagus nerve stimulation (aVNS) either alone or in addition to standard care** Electrical stimulation of the areas of the ear innervated by the vagus nerve, i.e. the concha or tragus, or specific mention of targeting the vagus nerve Product names: Various specific aVNS devices, including, but not limited to: ■ IB-Stim Auricular Stimulator and Bridge ■ NEMOS t-VNS device ■ Primary Relief or First Relief ■ Parasym ■ VIVO ■ taVNS Stimulator Various generic transcutaneous electrical nerve stimulation devices used for aVNS (e.g., the SNM-FDC01 device and the TENS 7000) MeSH and Emtree Terms: ■ Medline: Vagus Nerve Stimulation; Transcutaneous Electrical Nerve Stimulation; Electroacupuncture ■ Emtree: Transcutaneous electrical nerve stimulation; Vagus nerve stimulation **Excluded** ■ Transcutaneous stimulation of the cervical branch of the vagus nerve (this is not included in the submitting hospital application) ■ Stimulation of points on the ear that are not innervated by the vagus nerve ■ Studies with insufficient description of the intervention to be able to determine whether the vagus nerve was stimulated or targeted **Rationale** Informed by information provided by the submitting hospital, a scoping search of the literature, and published anatomic studies [46, 47]
Control	■ Sham aVNS (either alone or in addition to standard care) involving either inactive electrodes placed on the concha or tragus of the ear or active electrodes placed at sites on the ear that are not innervated by the vagus nerve (e.g., the ear lobe or helix), or another part of the body. ■ Condition-specific standard care MeSH and Emtree Terms: These were not used in the search strategy as they resulted in overly narrow search results. **Rationale** This was informed by clinical practice guidelines [16, 28-31]. When a site innervated by the vagus nerve was used, only inactive electrodes were considered an adequate sham treatment since it has been shown that even a 1 Hz aVNS stimulation can produce a therapetic effect [50].

Outcomes	
Efficacy	**Population One** ■ Changes in pain scores ■ Changes in analgesia or rescue medication usage ■ Length of hospital stay ■ Changes in specific postoperative endpoints, e.g. postoperative nausea and vomiting ■ Patient satisfaction **Population Two** ■ Changes in pain scores ■ Changes in physical functioning ■ Changes in symptom severity ■ Changes in rescue medication and concomitant pain treatment usage ■ Changes in emotional functioning ■ Changes in participant global ratings improvement ■ Changes in quality of life ■ Changes in pain interference ■ Changes in specific disease-related endpoints ■ Changes in psychological well-being, e.g., anxiety, sleep or fatigue ■ Changes in activities of daily living ■ Patient satisfaction **Excluded** Studies that did not report the primary outcome of pain **Rationale** Informed by a scoping search of the literature and consensus-based reporting standards [53]
Safety	■ Procedure-related adverse events, e.g. pain, bleeding or skin irritation ■ Adverse effects or complications, e.g. dizziness, headache or nausea ■ Serious adverse events
Study design	
Efficacy Safety	■ RCTs with a sample size ≥40 patients[20] **Excluded** Non-peer reviewed studies, narrative reviews, letters to the editor and author responses, non-randomised comparative studies, case series and case reports, conference abstracts **Rationale** The minimum sample size was based on power calculations from published RCTs [54-56]

Abbreviations: aVNS – auricular vagus nerve stimulation; MeSH – medical subject heading; RCT – randomised controlled trial

[20] A best evidence approach to study selection was taken, with recent, well-conducted systematic reviews selected preferentially, if available, over individual RCTs. Any systematic reviews identified would have been updated, where necessary, with primary studies published after the review's search end date.

3 Methods

3.1 Research questions

EUnetHTA Core Model® Version 4.2. für SR herangezogen

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model ® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [57].

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in vier Datenbanken

The systematic literature search was conducted on 7 December 2022 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- The International HTA Database (International Network of Agencies for Health Technology Assessment)

deutsche und englische RCTs

The systematic search was limited to articles published in English or German and in Medline and Embase to randomised controlled trials and systematic reviews.

insgesamt 1.531 Publikationen identifiziert

After deduplication, 954 citations were included. The specific search strategies employed can be found in the Appendix. Handsearching identified an additional four citations, resulting in a total of 1,531 hits. Manufacturers of the more common aVNS devices (NeurAxis, Inc., tVNS International GmbH and Vagustim) were contacted for information, but no new citations were identified.

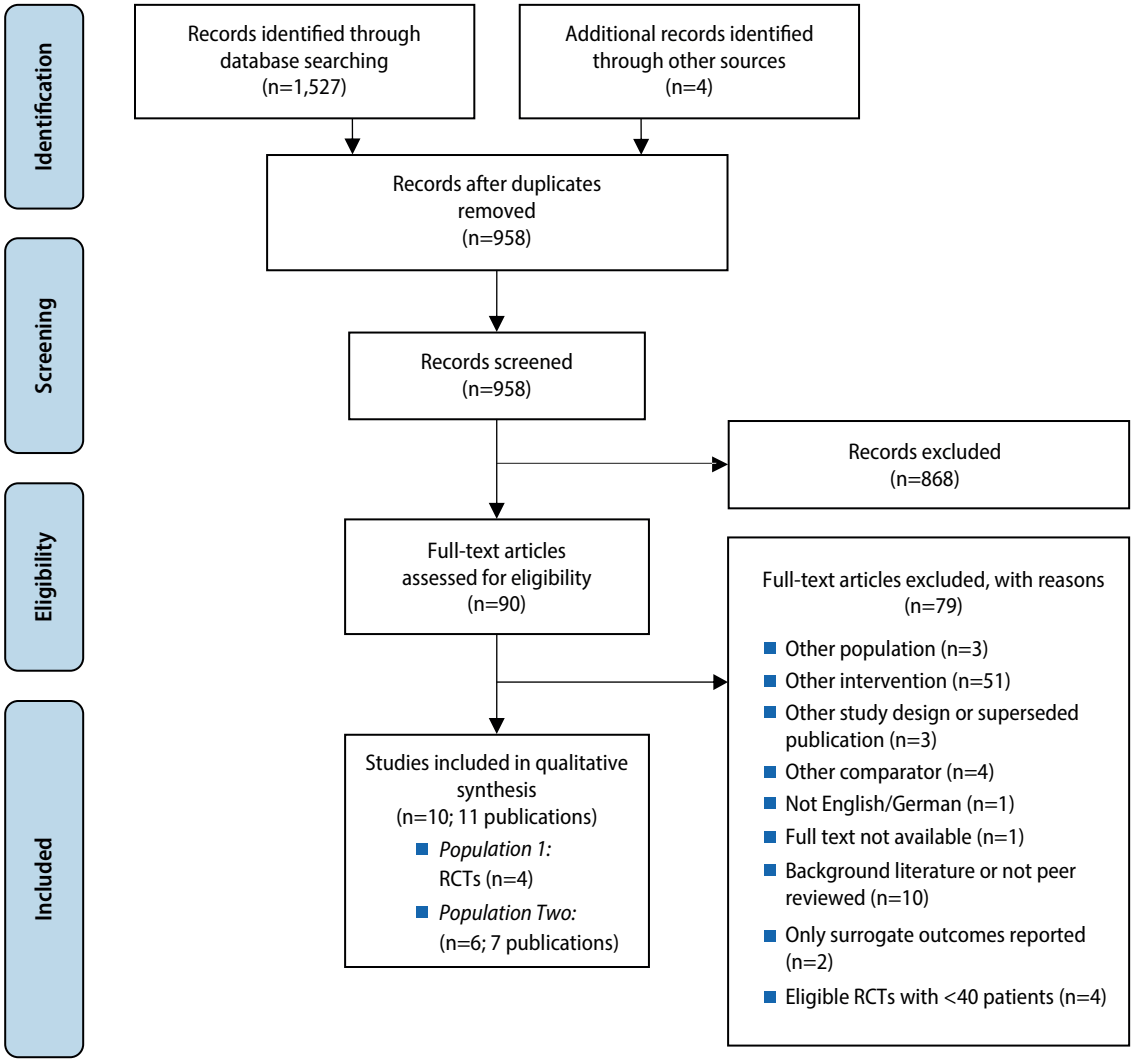
Suche nach laufenden Studien: insgesamt 87 Publikationen identifiziert

Three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP and EU Clinical Trials) were searched on 10 January 2023 to identify ongoing and unpublished studies, which resulted in 87 potentially relevant hits. The twelve relevant RCTs are summarised in the Appendix (Table A-1 and Table A-2).

3.2.2 Flow chart of study selection

Overall, 958 unique citations were identified from the literature searches. These references were screened by two researchers independently and, in cases of disagreement, a third researcher was involved to resolve the differences. The study selection process is displayed in Figure 3-1.

Literaturauswahl:
10 RCTs (11 Publikationen)



Abbreviations: RCTs – randomised controlled trials

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion aus Studien

Reviewers independently extracted relevant data for Population One (RAF) and Population Two (AS) from the included studies into data extraction tables that were designed and tested a priori. The data extraction tables were checked for accuracy by the reviewer not involved in the data extraction for the particular population (either RAF or AS), or by a third reviewer (VH).

Beurteilung der Studienqualität mit Cochrane RoB Tool (V.2)

One reviewer (AS) assessed the studies for internal validity and risk of bias using the Cochrane Risk of Bias 2 tool [58] and the quality of the data using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [59] (see Tables A-3 to Table A-12 in the Appendix). A second reviewer (VH) validated these assessments for accuracy. Any disagreements with respect to the data extraction or quality analyses were resolved by consensus.

3.2.4 Synthesis

qualitative Synthese der Evidenz

The questions were answered in plain text format with reference to GRADE evidence tables that are included in the Appendix (Table A-5 to Table A-12). Results are summarized in Table A-1 and Table A-2 in the Appendix.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

Critical outcomes

The following outcomes were defined as *critical* to derive a recommendation. Selection of critical outcomes was based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) core outcomes for chronic pain clinical trials [60, 61].

wesentliche Endpunkte Effektivität:

Populations 1 and 2

Population 1 & 2:

- ***Pain intensity*** is typically assessed with validated questionnaires such as the following [60].

  Schmerzintensität: gemessen mit versch. validierten Fragebögen

  Verbal rating scale (VRS): For VRS, several versions exist. Generally, the VRS for pain intensity is a ranked list of words that describe different pain levels and include extreme anchors and intermediate adjectives (e.g., no pain, mild pain, moderate pain and severe pain). For data analysis, each descriptor is coded with a numerical value (e.g., 0, 1, 2 and 3 for no pain, mild pain, moderate pain and severe pain, respectively). Survey participants must select the single descriptor that best reflects their pain level [60].

  VRS: Rangliste von Wörtern, die versch. Schmerzstufen beschreiben

  Visual analogue scale (VAS): For the VAS, respondents are asked to mark their pain level on a horizontal or vertical line that is usually 10 centimetres long. Anchors such as "no pain" and "worst pain imaginable" are labelled on the ends. The distance measured in millimetres from the beginning of the line (the "no pain" side) to the mark indicates the participant's level of pain [60].

  VAS: Markierung der Schmerzintensität auf einer horizontalen oder vertikalen Messlinie

  Numeric rating scale (NRS): This scale is the most commonly used measure for pain intensity in the clinical setting because it is easy to use and score. Study participants are asked to rate their pain intensity on a scale of 0 to 10 (or 20 or 100), with 0 usually representing "no pain" and 10 representing a descriptor indicating an extreme level of pain (e.g., "worst pain imaginable") [60].

  NRS: Bewertung der Schmerzintensität auf einer Skala von 1 bis 10

Population One only

nur Population 1:

- ***Analgesia consumption*** (time and amount of analgesic intake, usually measured by questionnaires)

  Analgetikaverbrauch,

- ***Use of rescue medication*** (medications that provide quick relief from acute symptoms, usually measured by questionnaires)

  Verwendung von Notfallmedikamenten

Population Two only

nur Population 2

- ***Physical functioning*** refers to one's ability to perform activities that require physical action, such as self-care, walking indoors or outdoors, or climbing stairs. The Short Form-36 (SF-36) is one of the most commonly used measures. It measures eight domains, including physical function. The physical function subscale consists of 10 items that ask participants, "Does your health condition now limit you in these activities? If yes, how much?" The activities range from bathing

  körperliche Funktion, meist erhoben durch SF-36-Fragebogen

or dressing to walking. For each item, there are three response options: 'yes, severely limited'; 'yes, somewhat limited'; and 'no, not limited at all'. The scores for each item are added together and converted into a scale from 0 to 100, with higher scores indicating better physical functioning [60].

Schweregrad der Symptome

- ***Symptom severity*** is typically assessed with various condition-specific symptom severity scales such as the Fibromyalgia Impact Questionnaire and the irritable bowel syndrome severity scoring system.

Important outcomes

wichtige Endpunkte: Population 1: Krankenhausaufenthaltsdauer, postop. Endpunktveränderungen, Pat.-zufriedenheit

Outcomes defined as *important* but not critical to derive a recommendation.

Population One

- ***Length of hospital stay***
- ***Changes in specific postoperative endpoints,*** such as postoperative nausea and vomiting
- ***Patient satisfaction***

Population 2: Einsatz von Analgetika & anderer Behandlungen

Population Two

- ***Rescue analgesic and concomitant pain treatment usage***

Schmerzstörungen

- ***Pain interference:*** The extent to which pain impedes one's ability to perform or participate in basic physical activities or more complex social activities. The Brief Pain Inventory and Multidimensional Pain Inventory both have pain interference scales with well-established measurement properties. There are also several condition-specific pain interference measures, primarily for musculoskeletal conditions [60].

emotionales Verhalten

- ***Emotional functioning:*** This refers to psychological distress or psychiatric comorbidity. Common measures include the Beck Depression Inventory and the Hospital Anxiety and Depression Scale [60].

allgemeine Verbesserungen

- ***Participant global ratings improvement:*** This integrates multiple aspects of the patient's treatment experience into a single assessment. There are several Likert scales that measure this, including the Patient Global Assessment of Treatment Satisfaction, the Patient-Rated Global Assessment of Response to Therapy and the Patient Global Impression of Change [60].

Lebensqualität

- ***Quality of life:*** The SF-36 is one of the most commonly used measures for this outcome.

4.1.2 Outcomes safety

wesentliche Endpunkte Sicherheit für Population 1 & 2:

The following outcomes were defined as *critical* to derive a recommendation for **populations 1 and 2:**

gerätebezogene unerwünschte Ereignisse

- ***Device-related adverse events (including tolerability issues and safety)*** are adverse events related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation or any malfunction of the investigational medical device as well as any event that is a result of a use error or intentional misuse [62].

andere unerwünschte Ereignisse = wichtige Endpunkte

Other important adverse events include, but are not limited to, non-device related adverse events.

Selection of critical outcomes was based on the IMMPACT core outcomes for chronic pain clinical trials [60, 61] and the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) adverse event reporting checklist [63].

Auswahl der kritischen Endpunkte basierend auf den IMMPACT-Kernergebnissen

4.2 Included studies

4.2.1 Included studies for effectiveness and safety

A total of 10 RCTs (11 publications) assessing the effectiveness of aVNS met the predefined inclusion criteria [54-56, 64-71]. Of these, only six reported on device safety or tolerability: four for acute pain [54-56, 64] and two for chronic pain [65, 66, 68]. Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Tables A-5 to A-12 in the Appendix.

10 RCTs (11 Publ.) für Effektivität und 6 RCTs für Sicherheit

Population One: Patients with acute postoperative pain

Population 1:

Four RCTs examined the use of aVNS for pain relief following laparoscopic or open small- or large-bowel resection [64], elective Cesarian delivery [54], elective mandibular third molar extraction [55] and anterior cruciate ligament reconstruction [56]. Two studies were conducted in the USA [54, 64] and one each in Austria [55] and China [56]. Percutaneous electrodes were used in three studies [54, 55, 64] and surface electrodes were used in one study [56]. The three percutaneous aVNS studies [54, 55, 64] targeted the auricular branch of the vagus nerve as well as peripheral projections of the auriculotemporal nerve, the great auricular nerve and the lesser occipital nerve. The transcutaneous VNS study targeted only the vagus nerve [56]. In one study each the treatment cycle was twelve hours [56] and 48 hours [55], whereas in the other two studies the patients received treatment for five days [54, 64]. aVNS was compared with inactive sham treatment (two studies [54, 55]), standard care (one study [54]), active stimulation at a site not innervated by the vagus nerve (one study [56]) and auricular acupuncture comprising needle electrodes connected to an inactive device (two studies [55, 64]). The active and sham treatments were used in addition to standard care in all four RCTs. The primary outcomes for the studies were total opioid [64] or acetaminophen [55] consumption, and incidence, duration, evoked pain (pain with movement) [54] and onset of rebound pain [56]. Although the devices were provided by the manufacturer in two studies [55, 64], none of the studies were formally sponsored by industry and none of the authors declared any conflicts of interest.

4 RCTs zu akuten postop. Schmerzen nach unterschiedlichen OPs

perkutane aVNS in 3 RCTs, tanskutane a VNS in 1 RCT

Behandlungsdauer: 12 Stunden bis 5 Tage

Vergleich mit Scheinbehandlung, Standardtherapie, aktiver Stimulation anderer Nervenstränge und aurikulärer Akupunktur

In total, 150 patients received aVNS, 87 underwent some form of sham treatment, 57 received auricular acupuncture and 20 received standard care. The patient groups were somewhat heterogeneous with respect to age, sex and other demographic parameters due to the different types of surgeries investigated. The mean age of participants ranged from 24 to 62 years across the four RCTs. One study [55] had more women and smokers in the aVNS group than in the sham or auricular acupuncture groups. There were no baseline differences between groups among the other three studies. The total length of follow-up after the start of treatment was 48 hours in two studies [55, 56] and five days in the other two [54, 64]. A single study also reported additional outcomes up to 30 days following the start of treatment [64].

insgesamt 314 Pat.

Ø Alter: 24 bis 62 Jahre

Follow-up von 2 bis 30 Tage

Population 2: 6 RCTs:

2 RCTs zu gastrointestinalen Störungen, 1 RCT zu episodischer Migräne, 2 RCTs zu Fibromyalgie und 1 RCT zu myofaszialen Schmerzen

Vergleich mit Scheinbehandlung, aktiver Stimulation anderer Nervenstränge und Kombination mit Standardbehandlung

Behandlungsdauer: 5 Tage bis 4 Wochen

insgesamt 363 Pat.

Ø Alter: 11 bis 75 Jahre

geringe Vergleichbarkeit der Studien in Bezug auf demografische Merkmale

Follow-up von 5 Tage bis 9,2 Wochen

Population Two: Patients with chronic pain

Six RCTs (7 publications) examined the use of aVNS for pain relief in patients with gastrointestinal disorders [65, 66, 69], episodic migraine [71], fibromyalgia [67, 68] and myofascial pain [70]. Two studies each were conducted in China [69, 71] and Turkey [67, 70], and one each in Norway [68] and the USA [65, 66]. Transcutaneous electrodes were used in all but one study [65, 66], with treatment durations varying from five days [70] to two [68] and four weeks [65-67, 69, 71]. Five of the studies placed the electrodes on the auricular concha, whereas the other study [65, 66] targeted the auricular branch of the vagus nerve as well as the peripheral projections of other cranial nerves. aVNS was compared with inactive sham treatment (one study [65, 66]), active stimulation at a site not innervated by the vagus nerve (three studies [68, 69, 71]), and exercise with or without trigger point compression (two studies [67, 70]). For three of the RCTs, the stated primary outcomes were change in abdominal pain scores [65, 66] reduction in the number of migraine days [71] and change in photoplethysmography-measured cardiac-vagal heart rate variability [68]. Two studies did not specify the primary outcomes [67, 70]. None of the studies were funded by device manufacturers and none of the study authors declared any conflicts of interest.

In total, 193 patients received aVNS, 121 underwent some form of sham treatment and 51 received standard care in the form of exercise therapy. One of the studies on abdominal-related pain only included children (aged 11 to 18 years), whereas the other only included adults (aged 18 to 75 years) [65, 66, 69]. Although the two studies on fibromyalgia focused on adults, one restricted inclusion to women only [67, 68]. Consequently, there was little comparability across the studies in terms of demographic characteristics. The mean age of participants ranged from 15 to 48 years across five RCTs (data were not available for one of the studies [71]). In one study, the aVNS group had more pain and worse physical function and social functionality on the SF-36 scale at baseline than the control group [67]. Another study had better scores in the aVNS group for the gastrointestinal subscale of the Compass-31 scale and worse scores for the energy-vitality and mental health subscales of the SF-36 at baseline than the control group [70]. The length of follow-up after the start of treatment was five days in one study [70], two to three weeks in two studies [65, 66, 68] and four weeks in three studies [67, 69, 71]. A single study also reported additional outcomes up to a median 9.2 weeks after the last week of treatment [65, 66].

4.3 Results

Results are reported separately for each outcome per comparison and by condition.

4.3.1 Population One: Patients with acute postoperative pain

Effectiveness

3 RCTs (Patient*innenanzahl (n) =209): aVNS vs. Scheinbehandlung:

aVNS versus sham treatment

Three RCTs reported outcomes for aVNS (n=122) and sham treatment (n=87) [54-56].

Pain[21]

Two RCTs found no difference between the two groups with respect to pain over five days of treatment following elective Cesarean delivery (n=40) [54] or the median duration of pain requiring analgesic treatment in the two days following surgical molar extraction (n=91) [55].

2 RCTs mit keinen s.s. Schmerzunterschieden zw. den Gruppen

In the third RCT (n=78), rebound pain in the first twelve hours after knee reconstruction surgery was less likely to occur in patients receiving aVNS (18% versus 41%; p=0.03) and lasted a shorter time (mean 1.7 versus 2.4 hours; p=0.002). The NRS scores were significantly lower in the intervention group.[22] There were no differences between these two groups with respect to pain measures over the subsequent 36 hours of follow-up.

s.s. geringeres Risiko und kürzere Zeit für Rebound-Schmerz nach ACL-Rekonstruktion zugunsten aVNS in 1 RCT

Analgesia consumption[21]

One study that provided statistical analysis of the comparison between aVNS and sham treatment found no differences in mean analgesia consumption up to 48 hours after mandibular third molar surgery [55].

1 RCT mit keinen s.s. Gruppenunterschieden bei der Einnahme von Analgetika

In a second RCT [54] the number of patients requiring opioids during their hospital stay after a Cesarean delivery was slightly lower in the aVNS group (60% of 20 patients), compared with sham treatment (80% of 20 patients), and the mean milligrams of morphine equivalent consumed was lower (51.1 versus 71.6). However, the statistical significance of these comparisons was not reported.

1 RCT mit geringerer Opioideinnahme bei Pat. mit aVNS nach einem Kaiserschnitt, s.s. nicht berichtet

A third RCT [56] found that the 39 patients receiving aVNS after knee reconstruction surgery were less likely to activate the patient-controlled analgesia pump in the first twelve hours than the 39 patients in the sham treatment group (2 versus 3; p=0.02). However, there was no discernible difference between the groups in the subsequent 36 hours.

s.s. weniger häufiges Drücken der Analgesiepumpe innerhalb 12 Stunden nach Knie-OP in 1 RCT

Use of rescue medication

There was no statistically significant difference in the use of rescue medication between the two treatment groups after surgical molar extraction in one study of 95 patients [55]. In contrast, another RCT of 78 patients noted that significantly fewer patients on aVNS required additional analgesics in the first twelve hours after anterior cruciate ligament reconstruction than those receiving sham treatment (26% versus 51%; p=0.004). However, this difference was not sustained in the following 36 hours [56].[21]

1 RCT mit s.s. weniger zusätzlich benötigte Analgetika bei Pat. in den ersten 12 Stunden nach Knie-OP

Postoperative nausea and vomiting

There was no statistically significant difference between aVNS and sham treatment in the proportion of patients experiencing nausea or vomiting two days after knee surgery [56].[23]

1 RCT mit keinen s.s. Unterschieden bei postop. Übelkeit und Erbrechen

aVNS versus non-electrical auricular acupuncture

Two RCTs reported outcomes for aVNS (n=91) and non-electrical auricular acupuncture (n=57) [55, 64].

2 RCTs (n=148): aVNS vs. nicht-elektrische Ohrakupunktur:

[21] **D0005** How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

[22] The actual scores could not be extracted from the graphical presentation provided in the report.

[23] **D0011** What is the effect of the technology on patients' body functions?

Pain[21]

1 RCT mit s.s. höheren Schmerzwerten an Tag 3 nach Darm-OP in aVNS-Pat.

One RCT [64] that followed up 52 patients over five days after major bowel surgery found no statistically significant differences in mean pain scores between the two treatments, except for a higher score on day 3 among the aVNS group (3.9 versus 2.7; p=0.03). The reason for this anomalous result was unclear.

1 RCT mit höherer Schmerzreduktion durch aVNS nach Weisheitszahnentfernung, s.s. nicht berichtet

The other RCT [55] reported that 49% of patients receiving aVNS perceived a reduction in pain after surgical molar extraction, compared with 36% in the non-electrical acupuncture group. However, a statistical analysis of this comparison was not provided. There was no difference between the two groups with respect to median duration of pain requiring analgesic treatment, mean analgesia consumption or use of rescue medication over the 2-day treatment period.

Analgesia consumption

1 RCT mit s.s. Verbesserungen beim Analgetikaverbrauch in Subgruppenanalysen für Pat. mit Darmresektion vs. Laparoskopie und Pat. > als 60 vs. jüngere Pat.

The two RCTs found no differences between aVNS and auricular acupuncture in mean analgesia consumption up to five days after surgery [55, 64]. One of these studies reported follow-up data on the proportion of patients requiring opioids in the 30 days following major bowel surgery and found no difference between the two groups [64]. However, a subgroup analysis of data from 52 patients who underwent open bowel resection found a benefit for aVNS with respect to analgesia consumption (p=0.03) and patients older than 60 years (p=0.01), in comparison with laparoscopic surgery and younger patients, respectively [64].[21]

Length of hospitalisation

1 RCT mit keinen s.s. Unterschieden zw. den Gruppen bei Länge der Hospitalisierung…

One study that measured this outcome found no statistically significant difference between percutaneous aVNS (n=28) and auricular acupuncture (n=24) in patients who had bowel resection surgery [64].[24]

Postoperative nausea and vomiting

…und postop. Übelkeit und Erbrechen nach Darm-OP

One study reported no statistically significant difference between aVNS (n=28) and auricular acupuncture (n=24) in the proportion of patients experiencing nausea or vomiting up to five days after major bowel surgery [64].[23]

Other outcomes

keine s.s. Unterschiede zw. den Gruppen nach Darm-OP

The 30-day hospital readmission rates were similar between patients receiving aVNS (n=28) and those who were administered auricular acupuncture (n=24) after bowel resection surgery [64].[24]

1 RCT mit Pat.-Zufriedenheit für aVNS nach Darm-OP: 8,2 von 10 Punkte

One study that measured patient satisfaction found that, overall, participants were satisfied with the aVNS device, reporting a mean score of 8.2 out of a possible 10 points [64]. However, it was unclear whether this measure pertained to only the active treatment group, or the acupuncture group as well.[25]

1 RCT (n=40): aVNS vs. Standardtherapie

aVNS versus standard care

One RCT reported outcomes for aVNS (n=20) and standard care (n=20) [54].

[24] **D0014** What is the effect of the technology on work ability?

[25] **D0017** Were patients satisfied with the technology?

Pain

There was no discernible difference in pain experienced at rest or with movement across days one through five of treatment among women following Cesarian delivery [54].[21]

1 RCT mit keinen s.s. Gruppenunterschieden bei Schmerzen nach einem Kaiserschnitt

Analgesia consumption

The number of patients who required opioids during their hospital stay was slightly lower in the aVNS group, compared with standard care (60% versus 70%), although the mean milligrams of morphine equivalent consumed was higher (51.1 versus 42.8) [54]. However, the statistical significance of these comparisons was not reported.[21]

1 RCT mit leicht geringerer Opioidaufnahme in aVNS-Gruppe nach einem Kaiserschnitt, s.s. nicht berichtet

Safety outcomes[26]

Percutaneous aVNS

perkutane aVNS:

Three studies reported on safety outcomes for percutaneous aVNS (n=111), auricular acupuncture (n=57) and sham (n=47) after two to five days of treatment [54, 55, 64].

3 RCTs (n=215)

In one study, a single patient receiving active treatment (n=20) withdrew due to device discomfort. No other procedure-related adverse events occurred. The mean rating for device tolerability in the 20 patients receiving aVNS ranged from 77% to 86% [54].

1 aVNS-Patientin beendete Studie vorzeitig wegen Geräteunverträglichkeit in einem RCT

In another RCT [55], 16% of patients receiving aVNS (n=63) complained of tiredness, compared with 18% in the auricular acupuncture group (n=33) and 4% who had sham treatment (n=27). Pain at the ear was more common during aVNS (11%) and acupuncture (12%) than during sham treatment (7%), although a statistical comparison of these results was not reported. The proportion of patients reporting treatment comfort as moderate to good was similar across the three treatment groups (range 90% to 94%).

16 % der aVNS Gruppe berichteten über Müdigkeit und 11 % über Schmerzen am Ohr in einem RCT

A third RCT reported that no adverse events occurred after either aVNS (n=28) or auricular acupuncture (n=24) [64].

1 RCT mit keinen Nebenwirkungen

Transcutaneous aVNS

transkutane aVNS

A single study reported on safety outcomes for aVNS (n=39) and sham treatment (n=39) in patients up to 48 hours after the start of a twelve-hour treatment session [56]. Although none of the patients in either group experienced light-headedness, ear irritation or tinnitus, one patient receiving sham treatment developed pruritus. The rate of sleep disturbance was significantly lower during aVNS, compared with sham treatment (31% versus 54%; p=0.03).

1 RCT mit Juckreiz als NW bei 1 Patient*in mit Scheinbehandlung & s.s. geringe Schlafstörungen in aVNS-Gruppe

[26] **C0008** How safe is the technology in comparison to the comparator(s)?

4.3.2 Population Two: Patients with chronic pain

Effectiveness

PAIN-RELATED GASTROINTESTINAL DISORDERS

aVNS vs. Scheinbehandlung bei abdominalen Schmerzen:

1 RCT (n=106): Ø 11 – 18 Jahre, 1 RCT (n=40): Erwachsene

aVNS versus sham treatment

Two RCTs reported outcomes for aVNS and sham treatment. One study reported on adults with constipation-predominant irritable bowel syndrome (21 treated with aVNS and 19 with a sham procedure) [69], while the other reported on children and adolescents (aged 11 to 18 years) with abdominal pain-related functional gastrointestinal disorders (57 treated with aVNS and 47 with a sham procedure), 49% of whom had irritable bowel syndrome [65, 66].

Pain[21]

1 RCT mit s.s. Reduktion der Schmerzen durch aVNS nach 3 und 9,2 Wochen bei Kindern und Jugendlichen (KiJu) mit abdominalen Schmerzen

Children and adolescents had a greater reduction in worst pain compared with sham after three weeks of treatment (least square means estimate of change 2.15, 95% confidence interval [CI] 1·37, 2·93; p<0.0001). The median Pain-Frequency-Severity-Duration composite score also decreased significantly in the aVNS group, compared with sham (mean decrease of 11·48, 95% CI 6·63, 16·32; p<0.0001) [65]. Both of these results were sustained over the extended follow-up period (median 9.2 weeks after the cessation of treatment). Reductions at least 30% in average pain and worst pain of were achieved in 58% and 60% of patients (n=48) following aVNS, compared with 29% and 22% of patients (n=45) after sham treatment.

Subgruppenanalyse des RCTs: s.s. Reduktion der Schmerzparameter durch aVNS bei KiJu mit Reizdarmsyndrom (RDS)

Similarly, a subgroup of children and adolescents with irritable bowel syndrome receiving aVNS (n=27) had a mean reduction in Pain-Frequency-Severity-Duration composite score of 11.53 (95% CI 3.62, 19.44; p=0.005) and in worst pain of 2.38 (95% CI, 1.13, 3.63; p=0.0002), compared with sham treatment (n=23) [66]. Reductions of at least 30% in worst abdominal pain were observed in 59% of patients with irritable bowel syndrome who received aVNS versus 26% of patients who received the sham device (p=0.02). However, these differences were not sustained at a median 9.2 weeks after the cessation of treatment, respectively.

1 RCT mit s.s. Verminderung des Schmerzes durch aVNS bei Erwachsenen mit RDS

In adults with irritable bowel syndrome, mean change in visual analogue pain score was significantly higher in the aVNS group than the sham group (69% decrease versus 18%; p=0.001), with 95% of 21 patients experiencing a reduction pain of at least 30% from baseline after aVNS, compared with 37% of 19 patients in the inactive treatment group (p<0.001) [69].

Symptom severity and function[21]

1 RCT mit s.s. Verbesserungen der Werte auf der Symptom-Response-Skala bei KiJu zugunsten aVNS nach 3 Wochen

Improvements in median Symptom Response Scale scores were higher after three weeks of aVNS than sham treatment in children and adolescents with gastrointestinal disorders (p=0.0003), with more patients having a score of at least two out of seven (73% versus 35%; p=0.0002) [65]. However, these between group differences were not evident at a median follow up of 9.2 weeks after treatment cessation. Function was also improved as result of aVNS, with a mean change in Functional Disability Inventory score of 36%, compared with no change after sham treatment (p-value not reported) [65].

A similar improvement was observed in the subgroup of patients with irritable bowel syndrome, where 78% of patients (n=27) had a Symptom Response Scale score of at least two out of seven after three weeks of aVNS treatment, compared with 39% in the sham group (n=23) (p=0.009); for a score of at least three the corresponding proportions were 67% and 22% (p=0.002) [66]. In the aVNS group, 81% of patients reported an overall improvement in symptoms, in contrast with 26% in the sham group (p=0.001).

Subgruppe des RCTs: s.s. Unterschiede bei der Symptom-Response-Skala und Verbesserungen der Symptome bei KiJu mit RDS

For adults with irritable bowel syndrome, the mean irritable bowel syndrome severity scoring system scores were significantly improved after aVNS, compared with sham treatment (mean 197.1 versus 289.5 after four weeks of treatment; p=0.001) [69].

1 RCT mit s.s. Verbesserung des Schweregrads von RDS bei Erwachsenen durch aVNs

Quality of life[27,28]

Adults with constipation-predominant irritable bowel syndrome had a significantly greater improvement in mean irritable bowel syndrome quality of life score after four weeks than those receiving sham treatment (mean score 83.2 versus 69.5 at end of follow-up; p=0.02) [69]. This was also the case for mean Self-Rating Anxiety Scale (mean score 38.7 versus 47.9 at end of follow-up; p=0.02) and Self-Rating Depression Scale (mean score 42.6 versus 50.7 at end of follow-up; p=0.01) scores [69].

1 RCT mit s.s. Unterschieden in Lebensqualität, Angst und Depression bei Erwachsenen mit RDS

In contrast, following the cessation of a four-week treatment program in youth, there was no difference between percutaneous aVNS and sham treatment in median State-Trait Anxiety Inventory for Children scores at a median 9.2 weeks' follow-up [65]. This was also the case for the subgroup of children and adolescents with irritable bowel syndrome [66].

1 RCT mit keinen s.s. Gruppenunterschieden bei der LQ bei KiJu mit abdominalen Schmerzen

Condition-specific outcomes[21, 29]

In one RCT, there was no difference between percutaneous aVNS and sham treatment in terms of the number of spontaneous bowel movements per week after three weeks among the subgroup of children and adolescents (n=50) with irritable bowel syndrome [66].

1 RCT mit keinen s.s. Unterschieden bei spontanen Darmentleerungen bei KiJu

In contrast, adults with constipation-predominant irritable bowel syndrome exhibited significant improvements in stool consistency (86% versus 16% of patients; p<0.001) and mean bowel movements per week after aVNS, compared with sham treatment (2.8 versus 0.9; p=0.001) [69].

1 RCT mit s.s. Verbesserung in Stulkonsistenz und Darmbewegungen bei Erwachsenen zugunsten von aVNS

Patient satisfaction

A single study that measured patient satisfaction six to twelve months after treatment with aVNS (n=43) and sham aVNS (n=30) found that the former group were more satisfied with their outcomes and were more likely to participate in another trial (79% versus 40%; p=0.007) [65].[25]

KiJu mit aVNS waren zufriedener mit Therapie als KiJu mit Scheinbehandlung

FIBROMYALGIA

aVNS versus sham treatment

One RCT reported outcomes for aVNS (n=28) and sham treatment (n=29) after two weeks of treatment [68].

1 RCT (n=57): aVNS vs. Scheinbehanldung bei Fibromyalgie

[27] **D0012** What is the effect of the technology on generic health-related quality of life?

[28] **D0013** What is the effect of the technology on disease-specific quality of life?

[29] **D0032** How does the technology modify the magnitude and frequency of morbidity?

Pain and symptom severity

ähnliche Ergebnissen zu Schmerzen und Symptomschwere, s.s. nicht berichtet

For aVNS compared with sham treatment, the mean changes in numeric rating scale scores (-0.82 versus -0.86), widespread pain index (-1.50 versus -1.69), symptom severity scale (-1.32 versus -1.21) and overall fibromyalgia severity (0-31 scale) (-2.82 versus -2.90) scores were relatively similar between the two groups. Statistical analyses were not available for these comparisons [68].[21,23]

1 RCT (n=52): aVNS + Bewegung vs. Bewegung bei Fibromyalgie

aVNS plus exercise versus exercise

One RCT reported outcomes for aVNS plus a home-based exercise program (n=27) versus the exercise program alone (n=25) after four weeks of treatment [67].

Pain

keine s.s. Gruppenunterschiede bei Schmerzen

There was no difference between the groups in terms of pain improvement [67].[21]

Quality of life and symptom severity

keine s.s. Gruppenunterschiede bei LQ und Symptomschwere

Adding aVNS to an exercise program made no difference to the degree of improvement in mean Fibromyalgia Impact Questionnaire, SF-36, Beck Anxiety Scale or Beck Depression Scale scores, compared with exercise alone [67].[21,27,28]

EPISODIC MIGRAINE WITHOUT AURA

1 RCT (n=59): aVNS vs. Scheinbehandlung bei Migräne ohne Aura

aVNS versus sham treatment

One RCT reported outcomes for active (n=33) and inactive (n=26) aVNS after four weeks of treatment [71].

Pain

s.s. Schmerzminderung zugunsten von aVNS

Patients experienced a greater degree of pain relief after aVNS, compared with baseline values, than those who received sham treatment (mean -17.4 versus -4.1; p=0.008) [71].[21]

Symptom severity

s.s. weniger und kürzere Migräne-episoden durch aVNS

Patients in the aVNS group experienced fewer (mean days -2.5 versus -0.7; p=0.02) and shorter (mean -1.5 versus -0.6; p=0.02; time unit was not specified) migraine episodes, compared with baseline, than those in the sham group [71].[21]

Quality of life

kein s.s. Gruppen-unterschiede bei LQ

Despite the improvement in pain relief observed in the aVNS group, there was no discernible difference between the two groups with respect to changes in mean Migraine Specific Quality-of-Life Questionnaire, Self-Rating Anxiety Scale or Self-Rating Depression Scale scores relative to baseline values over the four-week treatment course [71].[27,28]

MYOFASCIAL PAIN SYNDROME

1 RCT (n=53): aVNS + Standardbehandlung vs. Standardbehandlung bei myofaszialem Schmerzsyndrom

aVNS plus usual care (trigger point ischaemic compression and stretching exercises) versus usual care

One RCT reported outcomes for aVNS plus usual care (n=27) and usual care (n=26) [70].

Pain

After five days of transcutaneous aVNS plus usual care, mean pain scores were considerably lower, compared with baseline, than those who received usual care only (-2.77 versus -1.96; $p<0.001$).[21]

s.s. niedrigere Schmerzwerte durch aVNS

Functioning and quality of life

There were no statistically significant differences between the two groups with respect to changes in Compass-31 or SF-36 score, relative to baseline, after five days of treatment [70]. However, patients in the aVNS group exhibited a higher grip strength (mean change 2.1 versus 0.5 kg; $p=0.001$) than those receiving usual care.[23,27]

s.s. höhere Griffstärke durch aVNS

Condition-specific outcomes

Patients who received aVNS had a greater improvement in trigger point sensitivity (mean change 3.2 versus 1.6 kg/cm^2; $p<0.001$) than patients in the usual care group [70].[23]

s.s. Verbesserung bei Triggerpunkt-Sensibilität durch aVNS

Safety outcomes[26]

Percutaneous aVNS

One study reported on safety outcomes for percutaneous aVNS (n=57) and sham treatment (n=47) in children and adolescents with abdominal pain-related functional gastrointestinal disorders [65]. Three patients in each group complained of ear discomfort. Adhesive allergy was reported in one patient following aVNS and in two patients following sham treatment. No serious adverse events occurred in either group.

perkutane aVNS: 1 RCT (n=104): Ohrenbeschweren und Allergie gegen den Klebstoff in beiden Gruppen bei KiJu

Transcutaneous aVNS

A single study reported on safety outcomes for transcutaneous aVNS (n=28) and sham treatment (n=29) in adults with fibromyalgia [68]. One participant who received aVNS experienced chest discomfort and additional pain due to the nerve stimulation and discontinued treatment. No other adverse events occurred during the trial.

transkutane aVNS: 1 RCT (n=57): 1 Patient*in der aVNS-Gruppe brach Behandlung auf Grund von versch. Nebenwirkungen ab

5 Certainty of evidence

RoB: Cochrane Risk of Bias 2 tool

The risk of bias for individual studies was assessed with the Cochrane Risk of Bias 2 tool [58], and is presented in Table A-3 and Table A-4 in the Appendix.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [72] for each critical endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to resolve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [72].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE schema for the research questions can be found in the summary of findings tables below (Table 5-1 to Table 5-8) and in the evidence profile in the Appendix (Table A-5 to Table A-12).

5.1 Population One: Patients with acute postoperative pain

Studienqualität: niedriges bis hohes Verzerrungsrisiko

Study quality was assessed for critical outcomes: pain, analgesia and rescue medication usage and device related adverse events. The quality of the evidence ranged from low to high, with only one study rated as having a low risk of bias. All studies had some concerns regarding either allocation concealment or assessor blinding (in one case this was due to the nature of the intervention prohibiting blinding), and sometimes both. In addition, one study had an imbalance in baseline characteristics between the treatment groups that called into question the effectiveness of the randomisation process.

Stärke der Evidenz zu Effektivität und Sicherheit sehr niedrig bis hoch

The certainty of the evidence base for the comparison of aVNS with sham treatment ranged from very low to high. A single study contributed evidence of high certainty for all of the critical outcomes [56]. The heterogeneous outcome measures and time frames used to report pain response and analgesia and rescue medication usage, in addition to underlying concerns about the randomisation process, meant that much of the evidence was rated as low. However, the fact that the overall effect was similar across studies resulted in an upgrade in confidence that the studies were reporting a true effect despite their disparate measurement strategies. Confidence in the rates of device-related adverse effects was low because the inconsistency in numbers of adverse events across trials and their relatively minor nature suggested that they may not have been documented systematically. Similar problems in study execution plagued the evidence bases comparing aVNS with non-electrical auricular acupuncture or standard care, both of which had low certainty. The

single study comparing aVNS with standard care had limited precision due to its small sample size (n=40) [54].

Overall, the strength of evidence for the effectiveness and safety of aVNS in comparison with sham treatment, non-electrical auricular acupuncture or standard care in patients with acute postoperative pain was low.

Stärke der Evidenz zu Effektivität und Sicherheit insgesamt niedrig

5.2 Population Two: Patients with chronic pain

Study quality was assessed for the critical outcomes of pain, symptom severity, physical functioning and device-related adverse events. The quality of the evidence ranged from low to high, with most of the studies rated as having a moderate to high risk of bias. This was largely due to concerns regarding allocation concealment and assessor blinding (owing to the nature of the interventions in two studies [67, 70]), potential biases introduced by deviations from the intended treatments and differences in baseline health-related quality of life measures between groups in two studies, which may have biased the results [67, 70].

Studienqualität: niedriges bis hohes Verzerrungsrisiko

The evidence base for aVNS in patients with chronic pain-related gastrointestinal disorders comprised one study of high certainty for all of the critical outcomes [65, 66] and a smaller study of very low certainty [69]. The latter study had issues regarding allocation concealment, deviations from intended treatments and potential bias from outcome assessors possibly being aware of treatment allocation. The study's small sample size also introduced doubts about its precision. The single high quality study that reported on adverse events was downgraded to moderate certainty because of its sample size and the low number of events reported [65, 66].

Stärke der Evidenz von aVNS bei Pat. mit:

gastrointestinalen Erkrankungen: sehr niedrig bis hoch

The evidence base for patients with fibromyalgia included one study of moderate certainty, which had limited precision due to its small size [68], and one study of very low certainty [67]. The former study reported both safety and effectiveness data. The lower rated open label study only reported effectiveness outcomes and suffered from concerns about allocation concealment and deviations from intended interventions, small size, and imbalances in baseline health-related quality of life measures between groups.

Fibromyalgie: moderat bis hoch

The single study on patients with chronic episodic migraine [71] had some concerns about allocation concealment but was otherwise deemed to have moderate certainty.

episodischer Mirgäne: moderat

The single study on patients with chronic myofascial pain syndrome was rated as having a very low certainty due to its open label design, small sample size and baseline imbalances in health-related quality of life measures between groups, which casts doubt on the veracity of the randomisation process.

myofaszialem Schmerzsyndrom: sehr niedrig

Overall, the strength of evidence for the effectiveness and safety of aVNS was low to moderate for chronic pain-related gastrointestinal disorders, low for chronic fibromyalgia, moderate for chronic episodic migraine and very low for chronic myofascial pain syndrome.

Stärke der Evidenz zu Effektivität und Sicherheit: sehr niedrig - moderat

*Table 5-1: Summary of findings table for **aVNS versus sham treatment** in patients with acute postoperative pain*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference	Number of participants (studies)	Quality	Comments
	Risk with sham treatment	Risk with intervention					
Pain							
After 12 hours of treatment	NA	NA	Not estimable	NRS scores were significantly lower in the intervention group (data not reported)	78 (1)	⊕⊕⊕⊕ High	Favours intervention (p<0.05) No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.
After 2-5 days of treatment	NA	NA	Not estimable	Measured using various scales over different time periods	131 (2)	⊕⊕◯◯ Low [a]	No apparent difference between groups in either study. Statistical analysis of comparison not reported in one study.
Analgesia consumption							
No. of times pressed analgesia pump over 12 hours of treatment	NA	NA	Not estimable	Intervention: 2 Sham: 3	78 (1)	⊕⊕⊕⊕ High	Favours intervention (p=0.02) No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.
Over 2-5 days of treatment	NA	NA	Not estimable	Measured using various units over different time periods	127 (2)	⊕⊕◯◯ Low [a]	No apparent difference between groups in either study. Statistical analysis of comparison not reported in one study.
Use of rescue medication							
Over 12 hours of treatment	51 per 100	26 per 100	RR 0.50 (0.27, 0.93)	-	78 (1)	⊕⊕⊕⊕ High	Favours intervention (p=0.004) No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.
Over 2-5 days of treatment	19 to 80 per 100	19 to 60 per 100	Not estimable	-	135 (2)	⊕⊕◯◯ Low [a]	No difference between groups in either study.
Device-related adverse events (after 2-5 days of treatment) [c]	8 per 100	15 per 100	RR 1.81 (0.79, 4.15)	-	208 (3)	⊕◯◯◯ Very low [b]	No difference between groups Adverse events included pruritus, ear discomfort and tiredness. Unclear if patients experienced more than one event.

Abbreviations: *CI – confidence interval; NA – not applicable; NRS: numeric rating scale; RR – risk ratio*

Explanations

[a] *Serious concerns regarding randomisation process and allocation concealment in all trials. Imbalance in baseline characteristics between groups in one study [55]. Upgraded certainty rating due to consistency of effect across studies despite varied outcome measures.*

[b] *Very low numbers of events in some studies.*

[c] *Since the types of adverse events were similar for percutaneous and transcutaneous, the event rates for each were combined.*

*Table 5-2: Summary of findings table for **aVNS versus non-electrical auricular acupuncture** in patients with acute postoperative pain*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference	Number of participants (studies)	Quality	Comments
	Risk with auricular acupuncture	Risk with intervention					
Pain (after 2-5 days of treatment)	NA	NA	Not estimable	Measured using various scales over different time periods	151 (2)	⨁⨁◯◯ Low [a]	No difference between groups in either study
Analgesia consumption (over 2-5 days of treatment)	NA	NA	Not estimable	Measured using different units over different time periods	143 (2)	⨁⨁◯◯ Low [a]	No difference between groups in either study
Use of rescue medication (over 2 days of treatment)	18 per 100	19 per 100	RR 1.08 (0.44, 2.62)	-	97 (1)	⨁⨁◯◯ Low [a]	No difference between groups
Device-related adverse events (after 2-5 days of treatment)	18 per 100	19 per 100	RR 1.08 (0.44, 2.62)	-	151 (2)	⨁⨁◯◯ Low [a, b]	No difference between groups in either study

Abbreviations: *CI = confidence interval; NA = not applicable; RR = risk ratio*

Explanations

[a] *Some concerns about allocation concealment and imbalance in baseline characteristics between the treatment groups in both trials.*

[b] *Some inconsistency in numbers of adverse events across trials suggests that they may not have been documented systematically, particularly given their relatively minor nature.*

*Table 5-3: Summary of findings table for **aVNS versus standard care** in patients with acute postoperative pain*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference mean [SD]	Number of participants (studies)	Quality	Comments
	Risk with standard care	Risk with intervention					
Pain (numeric rating scale) after 72 hours of treatment	NA	NA	Not estimable	Intervention: 4.6 [2.3] Standard care: 4.2 [2.3]	40 (1)	⊕⊕◯◯ Low [a]	No apparent difference between groups for any of the outcomes. Statistical analysis of comparison not reported in the study.
Analgesia consumption (MME) over 5 days of treatment	NA	NA	Not estimable	Intervention: 51.1 [56.6] Standard care: 42.8 [44.0]	40 (1)	⊕⊕◯◯ Low [a]	
Use of rescue medication (opioids) over 5 days of treatment	70 per 100	60 per 100	RR 0.86 (0.57, 3.14)	-	40 (1)	⊕⊕◯◯ Low [a]	No difference between groups
Device-related adverse events after 5 days of treatment	0	5 per 100	RR 0.86 (0.54, 1.36)	-	40 (1)	⊕⊕◯◯ Low [a]	No difference between groups

Abbreviations: *CI = confidence interval; MME = milligram morphine equivalent; NA = not applicable; RR = risk ratio; SD = standard deviation*

Explanations

[a] *Some concerns about allocation concealment and assessor blinding (open label study due to nature of comparator). Small sample size limits precision.*

Table 5-4: Summary of findings table for ***aVNS versus sham treatment*** *in patients with* ***chronic pain-related gastrointestinal disorders***

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference mean [SD]	Number of participants (studies)	Quality	Comments
	Risk with sham treatment	Risk with intervention					
Pain Youth (11-18 years) PFSD median 9.2 weeks after end of 3-week treatment session)	NA	NA	Not estimable	Median after treatment Intervention: 8.4 (IQR 3.2, 16.2) Sham: 15.2 (IQR 4.4, 36.8)	104 (1)	⊕⊕⊕⊕ High	Favours intervention (p=0.02) Result after 3 weeks of treatment also favours intervention (p<0.0001).
Adults (≥18 years) Visual analogue scale after 4 weeks of treatment	NA	NA	Not estimable	Mean change Intervention: -3.1 [2.2] Sham: -1.1 [1.1]	40 (1)	⊕◯◯◯ Very low [a]	Favours intervention (p=0.001)
Physical functioning Youth (11-18 years) FDI median 9.2 weeks after treatment cessation	NA	NA	Not estimable	Mean change Intervention: ↓36% Sham: 0%	104 (1)	⊕⊕⊕⊕ High	Appears to favour intervention. Statistical analysis of comparison not reported in the study.
Symptom severity Youth (11-18 years) SRS after 3 weeks of treatment	NA	NA	Not estimable	Median after treatment Intervention: 3 (IQR 1.0, 4.8) Sham: 1 (IQR 0.0, 2.3)	104 (1)	⊕◯◯◯ Very low [a]	Favours intervention (p=0.0003) Higher score is better No difference between groups median 9.2 weeks after treatment cessation (data not reported)
Adults (≥18 years) IBS-SSS score after 4 weeks of treatment	NA	NA	Not estimable	Mean after treatment Intervention: 197.1 [39.6] Sham: 289.5 [94.4]	40 (1)	⊕⊕⊕⊕ High	Favours intervention (p=0.001) Lower score is better
Device-related adverse events [c] Youth (11-18 years) after 3 weeks of treatment	11 per 100	7 per 100	RR 0.66 (0.19, 2.32)	-	104 (1)	⊕⊕⊕◯ Moderate [b]	No difference between groups Adverse events included ear discomfort and adhesive allergy. One event of syncope due to needle phobia in sham group was not included in the RR calculation.

Abbreviations: *CI = confidence interval; FDI: Functional Disability Inventory; IBS-SSS: irritable bowel syndrome severity scoring system; IQR: interquartile range; NA = not applicable; PFSD: Pain-Frequency-Severity-Duration; RR = risk ratio; SD = standard deviation; SRS = Symptom Response Scale*

Explanations

[a] *Some concerns about allocation concealment, bias due to deviations from intended interventions and bias in outcome measures due to outcome assessors being aware of treatment allocation. Single blind study design and small sample size raises concerns regarding precision.*

[b] *Small RCT and low number of events.*

[c] *Since the types of adverse events were similar for percutaneous and transcutaneous, the event rates for each were combined.*

*Table 5-5: Summary of findings table for **aVNS versus sham treatment** in patients with **chronic fibromyalgia** at last follow-up (after two weeks of treatment)*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference	Number of participants (studies)	Quality	Comments
	Risk with sham treatment	Risk with intervention					
Pain **Numeric rating scale**	NA	NA	Not estimable	Mean change Intervention: -0.82 Sham: -0.86	57 (1)	⊕⊕⊕○ Moderate [a]	No apparent difference between groups for either of the outcomes. Statistical analysis of comparisons not reported in the study.
Widespread pain index	NA	NA	Not estimable	Mean change Intervention: -1.50 Sham: -1.69	57 (1)	⊕⊕⊕○ Moderate [a]	
Symptom severity (symptom severity scale)	NA	NA	Not estimable	Mean change Intervention: --1.32 Sham: -1.21	57 (1)	⊕⊕⊕○ Moderate [a]	No apparent difference between groups for any of the outcomes. Statistical analysis of comparison not reported in the study.
Device-related adverse events	0	4 per 100	RR 3.10 (0.13, 73.12)	-	57 (1)	⊕⊕⊕○ Moderate [a]	No difference between groups The single adverse event involved chest discomfort and additional pain, leading to patient withdrawal.

Abbreviations: *CI = confidence interval; NA = not applicable; RR = risk ratio.*

Explanations

[a] *Small sample size limits precision*

*Table 5-6: Summary of findings table for **aVNS plus exercise versus exercise** in women with **chronic fibromyalgia** at last follow-up (after four weeks of treatment)*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference mean [SD]	Number of participants (studies)	Quality	Comments
	Risk with exercise	Risk with intervention					
Pain (visual analogue scale)	NA	NA	Not estimable	Mean after treatment Intervention: 2.6 [1.91] Exercise: 3.5 [1.73]	52 (1)	⊕○○○ Very low [a]	No difference between groups (p=0.08) Study only included women
Symptom severity (Fibromyalgia Impact Questionnaire score)	NA	NA	Not estimable	Mean after treatment Intervention: 37.3 [19.48] Exercise: 41.9 [18.15]	52 (1)	⊕○○○ Very low [a]	No difference between groups (p=0.4) Lower score is better Study only included women

Abbreviations: *CI = confidence interval; NA = not applicable; SD = standard deviation*

Explanations

[a] *Open label study due to nature of interventions. Some concerns about allocation concealment and deviations from intended interventions. Imbalance in baseline health-related quality of life measures between groups. The combination of these factors raises concerns regarding precision.*

*Table 5-7: Summary of findings table for **aVNS versus sham treatment** in patients with **chronic episodic migraine** without aura at last follow-up (after four weeks of treatment)*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference	Number of participants (studies)	Quality	Comments
	Risk with sham treatment	Risk with intervention					
Pain (visual analog scale)	NA	NA	Not estimable	Mean change Intervention: -17.4 Sham: -4.1	59 (1)	⊕⊕⊕○ Moderate [a]	Favours intervention (p=0.008)
Symptom severity **Migraine days**	NA	NA	Not estimable	Mean change Intervention: -2.5 Sham: -0.7	59 (1)	⊕⊕⊕○ Moderate [a]	Favours intervention (p=0.02)
Migraine duration	NA	NA	Not estimable	Mean change Intervention: -1.5 Sham: 0.4	59 (1)	⊕⊕⊕○ Moderate [a]	Favours intervention (p=0.02) Time unit not specified in study

***Abbreviations**: CI = confidence interval; NA = not applicable*

Explanations

[a] *Some concerns about allocation concealment.*

*Table 5-8: Summary of findings table for **aVNS plus usual care versus usual care** in patients with **chronic myofascial pain syndrom**e at last follow-up (after five days of treatment)*

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference mean [SD]	Number of participants (studies)	Quality	Comments
	Risk with usual care	Risk with intervention					
Pain (visual analogue scale)	NA	NA	Not estimable	Mean change Intervention: -2.77 Usual care: -1.96	53 (1)	⊕○○○ Very low [a]	Favours intervention (p<0.001)
Physical functioning (grip strength, kg)	NA	NA	Not estimable	Mean change Intervention: 2.1 Usual care: 0.5	53 (1)	⊕○○○ Very low [a,b]	Favours intervention (p=0.001)
Symptom severity (Compass-31 score)	NA	NA	Not estimable	Mean change secretomotor subscale Intervention: -0.88 [1.295] Usual care: -0.12 [0.816]	53 (1)	⊕○○○ Very low [a]	Favours intervention (p=0.01) for secretomotor subscale only Comparisons for the other five subscales were not statistically significant

Abbreviations: *CI = confidence interval; NA = not applicable; SD = standard deviation*

Explanations

[a] *Open label study due to nature of interventions. Slight imbalance in baseline symptom severity and health-related quality of life measures between groups. The combination of these factors raises concerns regarding precision.*

[b] *Physical grip strength measures only one aspect of physical function.*

6 Discussion

6.1 Summary of findings

6.1.1 Efficacy

Population One: Acute postoperative pain

perkutane aVNS: keine Verbesserungen in Schmerzen und Schmerzmittelkonsum bei Kaiserschnitt, operativer Weisheitszahnentfernung und größeren kolorektalen OPs

Limited evidence from two RCTs [54, 55] suggested that the use of percutaneous aVNS plus standard care over a period of two to five days following elective Cesarian delivery or surgical molar extraction was not more effective than sham treatment plus standard care or standard care alone in terms of reducing pain, analgesia consumption or rescue medication usage (low certainty evidence from one RCT each). Similar results were observed in two additional RCTs (low certainty evidence) that compared percutaneous aVNS with auricular acupuncture over a 2- to-5-day treatment cycle in patients who had undergone major colorectal surgery or surgical molar extraction [55, 64]. One of these studies [64] also reported no differences between active neurostimulation and auricular acupuncture with respect to occurrence of postoperative nausea and vomiting, length of hospital stay and 30-day readmission rates [64].

s.s. Unterschiede zugunsten transkutane aVNS bei Rekonstruktion des vorderen Kreuzbandes (ACL) bei Schmerzmiderung, Schmerzmittelkonsum und Schlafstörungen

A single RCT (high certainty evidence) examined the effects of transcutaneous aVNS in ameliorating rebound pain after femoral nerve block in patients undergoing anterior cruciate ligament reconstruction [56]. The results indicated that aVNS was superior to sham in reducing pain (the actual pain scores could not be extracted from the graphical presentation provided in the report), analgesia consumption (↓33%), rescue medication usage (50% less risk) and sleep disturbance (57% less risk) during the twelve hours of treatment following surgery.

Population Two: Chronic pain

Pain-related gastrointestinal disorders

gastrointestinale Beschwerden: statistisch signifikante Verbesserungen von Schmerzen und Symptomschwere bei Kindern, Jugendlichen und Erwachsenen

Clinically and statistically significant improvements in pain and symptom severity were reported in youth with pain-related gastrointestinal disorders (aged 11-18 years; high certainty evidence from one RCT [65]) and adults with constipation-predominant irritable bowel syndrome (very low certainty evidence from one RCT [69]) during a three- to four-week regimen of percutaneous or transcutaneous aVNS. Physical functioning was also significantly improved in youth, while the adult group experienced improvements in quality of life, anxiety, depression, number of weekly spontaneous bowel movements and stool consistency. Although anxiety and number of weekly spontaneous bowel movements were measured in the youth group, there were no statistically significant differences observed between the two treatment groups in these outcomes. The reductions in pain were sustained in the 11- to 18-year-old patients a median of 9.2 weeks after treatment cessation. A subgroup of children and adolescents with irritable bowel syndrome had similar improvements in pain and symptom severity [66].

Episodic migraine without aura

Transcutaneous aVNS significantly reduced pain (↓35%) in patients with episodic migraine without aura in one RCT [71] (moderate certainty evidence), but this did not translate into significantly different improvements in quality of life or psychometric measures between the two groups relative to baseline values over the four-week course of treatment.

transkutane aVNS vermindert s.s. den Schmerz bei episodischer Migräne ohne Aura

Fibromyalgia

Evidence from one RCT [68] (moderate certainty evidence) suggested that transcutaneous aVNS was no better than sham treatment in reducing pain or symptom severity in patients with chronic fibromyalgia. Similarly, supplementing a home-based exercise program with transcutaneous aVNS for women with chronic fibromyalgia provided no additional benefit over the exercise program alone with respect to pain, symptom severity, quality of life or psychometric measures (very low certainty evidence) [67].

transkutane aVNS bei Fibromyalgie zeigt keine Unterschiede zu anderen Behandlungsformen

Myofascial pain syndrome

A single RCT [70] (low certainty evidence) found that the addition of transcutaneous aVNS to a conventional regimen of trigger point ischaemic compression and stretching exercises significantly improved pain and grip strength in patients with myofascial pain syndrome, compared with the conventional care regimen alone. This did not translate into statistically significant changes in quality of life between the two treatments, but the result may have been confounded by baseline differences in quality of life and symptom severity measures.

transkutane aVNS verbessert im Vergleich zur Standardtherapie signifikant den Schmerz und die Griffkraft bei myofazialem Schmerzsyndrom

6.1.2 Safety

The rates device-related adverse events in the six RCTs that reported them (four for acute pain [54-56, 64] and two for chronic pain [65, 68]) were similar between the treatment groups and ranged from 0% to 19%. These encompassed minor complications such as ear discomfort, tiredness and adhesive allergy.

gerätebezogene unerwünschte Ereignisse: 0 – 19 %

6.1.3 Interpretation and limitations of the evidence

The minimal clinically important difference (MCID) is defined as the smallest change in an outcome that a patient would perceive as clinically meaningful [73]. For acute pain, there is a lack of consensus regarding the size of the MCID because it is context specific and influenced by baseline pain—patients with higher baseline pain need a larger pain reduction to perceive relief [74]. For chronic pain, the IMMPACT group define the MCID as an improvement of at least 30% in self-reported pain and function [75]. The MCID for chronic pain is influenced by baseline pain and, to a lesser extent, the operational definition of relevant pain relief and the underlying clinical condition [76].

IMMPACT-Gruppe: 30 % Reduktion in selbstberichteten Schmerz = minimaler klinisch relevanter Unterschied bei chronischen Schmerzen

By these criteria, the improvements in pain observed after femoral nerve block for knee surgery and in patients with chronic pain-related gastrointestinal disorders, episodic migraine and myofascial pain syndrome were clinically important. However, one problem in interpreting results of studies that report mean or differences in outcomes related to pain or function is that they do not distinguish between situations where some patients experience a very good outcome and others experience no benefit and situations where patients generally experience a small but similar average result [73]. However, the studies on chronic pain-related gastrointestinal disorders avoided this issue

klinisch relevanter Unterschied bei einigen eingeschlossenen Studien feststellbar

by reporting data on changes in worst score pain and the proportion of patients experiencing a reduction in pain of at least 30% from baseline, both of which were significantly better after aVNS than sham treatment.

eingeschränkte Vergleichbarkeit der Studien zu akuten postop. Schmerz:

unterschiedliche Arten von Operationen und postop. Schmerzbehandlungsprotokollen

In the four studies on acute postoperative pain, different types of surgeries and postoperative pain management protocols were undertaken, limiting their comparability. For example, one of the included RCTs [64] deviated from the standard multimodal pain strategy used after bowel resection by avoiding non-steroidal anti-inflammatory drugs and regional anaesthesia and relying only on opioid analgesia, with the addition of acetaminophen, in order to better quantify any changes in opioid use. This study, unlike the other RCTs, also used an enhanced recovery after surgery pathway, which could have affected the length of stay and offset the analgesic effects of aVNS [77]. Since the nature of pain and the efficacy of analgesics varies after different types of surgery, the results of the included studies on acute postoperative pain cannot sensibly be extrapolated to patients undergoing other types of surgery [78, 79].

Effekt zu Rebound-Schmerz für längere postop. Phase (> 12 Stunden) unklar, auf Grund der kurzen Anwendungszeit von aVNS

Peripheral nerve blocks are commonly used in orthopaedic surgery to reduce perioperative pain and opioid consumption. However, within 24 hours of receiving a nerve block approximately 50% of patients experience rebound pain, which is an acute postoperative pain (numerical rating scale score ≥7) [56]. Rebound pain typically occurs around twelve hours after surgery, once the nerve block has resolved, and is associated with impaired recovery, increased opioid consumption, side effects of opioid overdose and sleep disturbance [80]. Risk factors for rebound pain include younger age, female sex, a higher preoperative pain score and having undergone bone surgery [81, 82]. While there are currently no effective preventive measures or treatments for rebound pain, a single RCT [56] demonstrated that transcutaneous aVNS may be able to ameliorate its severity and duration and reduce pain-related sleep disturbance. However, since the treatment was only applied during the first twelve hours after knee surgery, it is unclear what the effects would be if the treatment was continued further into the postoperative period. The lack of difference between aVNS and sham treatment over the 36 hours following treatment cessation further supports that the observed effects were related to active neural stimulation.

begrenzte Informationen zu Sicherheit

The limited safety data and small number of studies do not allow any extrapolation between the stimulation parameters used and the rates of adverse events reported. Since the complications were relatively minor, it is possible that the reported event rates were low because they were not systematically documented. However, a recent systematic review of 51 studies (1,322 humans) in healthy volunteers and patients using a variety of transcutaneous and percutaneous VNS devices (25 studies used auricular devices) found similar types and rates of complications [39].

6.2 Evidence gaps and ongoing studies

unterschiedliche Bedingungen, Stimulationseinstellungen und Länge der Behandlung

unklar, welche der verschiedenen Nervenstränge in der Ohrmuschel während aVNS stimuliert wurden

The variation in stimulation settings and length of treatment cycles employed as well as conditions studied across the included studies is indicative of the exploratory nature of aVNS in pain control. To introduce some homogeneity in the evidence base, the included studies were restricted to only trials that applied electrodes to areas of the ear innervated by the vagus nerve or specifically mentioned targeting the vagus nerve. However, three of the four studies on acute pain [54, 55, 64] and one on chronic pain [65, 66] targeted the auricular branches of other nerves as well. There is some conjecture as to whether the assumption that the cymba concha is innervated solely by the auricular vagus nerve is robust given the small number of anatomic studies it is

based on and the fact that it may not apply in a larger population of ethnically diverse individuals [38, 46, 47]. Furthermore, six of the ten included studies used transcutaneous aVNS, which produces a more diffuse stimulation field and may inadvertently stimulate non-vagal nerves [37, 45]. The aVNS studies also generally relied on stimulation parameters that are similar to those used for implantable VNS [38] even though there is some doubt as to whether these parameters are optimal, given the differences in target fibre type, fibre orientation, and electrode design and contact area between these treatments [83]. All of these factors underline the fact that it is not completely clear from the evidence which of several nerve trunks innervating the auricle are being activated during aVNS, and what the optimal stimulation parameters might be for specific indications.

Schwierigkeiten der Implementierung einer aktiven Scheinbehandlung als Vergleich zu aVNS

The limited understanding of local target engagement and mechanism of action of aVNS also means that it is difficult to implement an active sham treatment that produces satisfactory perception in the therapeutic group without engaging a therapeutic pathway (Table 6-1). This was demonstrated when a study [50] inadvertently found that a one Hz aVNS stimulation, which has been used as a sham treatment, was more effective at improving symptoms than 25 Hz aVNS in patients with chronic migraine.

Table 6-1: Advantages and disadvantages of types of controls used in aVNS trials [38]

Pros	Cons
Placebo	
■ Strong patient blinding in parallel study designs in acute setting ■ Strong investigator blinding	■ Poor blinding in crossover design when patient experiences paraesthesia in the active group
Pharmacological or no intervention	
-	■ Potential for large placebo effect ■ Poor investigator blinding
Location sham	
■ Strong patient blinding in acute setting	■ Patient blinding prone to compromise in chronic setting ■ Poor investigator blinding ■ Recruits potentially therapeutic nerves
Waveform shama[a]	
■ Strong patient blinding ■ Strong investigator blinding	■ Recruits potentially therapeutic nerves

[a] *Not used in any of the included studies*

Ergebnisse nicht auf andere Personengruppen übertragbar

Overall these studies provide evidence that aVNS may be therapeutic for some pain conditions, but the results cannot be extrapolated beyond these specific medical conditions. Most of these effects were only observed in a single RCT and require further validation, particularly given the limitations in the evidence base noted above and that the execution of some studies cannot rule out contributions from placebo effects. In the cases where aVNS does have a clinical benefit, the studies only provide a guide as to the stimulation settings that may be appropriate in that population group, and in the case of relieving acute rebound pain following femoral nerve block the optimal timing of aVNS treatment is still unknown.

6.2.1 Acute postoperative pain: ongoing studies

laufende Studien: 1 RCT zu akuten, postoperativen Schmerz (600 Pat)

One RCT with a primary completion date of July 2024 will assess the use of aVNS versus sham treatment for the relief of pain in 600 patients undergoing arthroplasty in China. The study has not yet started to recruit patients.

6.2.2 Chronic pain: ongoing studies

6 RCTs zu chronischen muskuloskelettalen Erkrankungen (36 – 148 Pat)

Of the 11 ongoing RCTs identified, six will examine the use of aVNS to relieve pain in chronic musculoskeletal conditions such as low back pain (1), erosive hand osteoarthritis (1), neck pain (1), temporomandibular joint dysfunction (1) and knee osteoarthritis (2). The comparators for these studies encompass sham with or without some form of standard physiotherapy intervention (e.g., exercise or ultrasound therapy). The study sizes range from 36 to 148. Two of the RCTs were recently completed, three are either ongoing or enrolling patients and one has yet to recruit patients.

5 RCTs zu einer Reihe von versch. Schmerzzuständen (47 – 116 Pat)

The other five RCTs will assess the use of aVNS for a variety of pain-related conditions, including radiotherapy-related neuropathic pain, post-stroke complex regional pain syndrome, cyclic vomiting syndrome, chronic pelvic pain and chronic pain related to opioid withdrawal. The studies will compare aVNS with sham treatment or some form of condition-specific standard care in populations of 47 to 116 patients. Three of these studies are in or have just completed the recruiting phase and one has yet to start. The primary completion dates cited for these studies range from March 2021 to October 2027.

6.3 Limitations of the assessment

Ausschluss von RCTs mit weniger als 40 Pat.

und

RCTs mit unzureichenden oder fehlenden Informationen darüber, welcher Ohrennerv stimuliert wurde

Due to the amount of RCT evidence identified, lower levels of evidence or RCTs with fewer than 40 participants were excluded. The latter criterion resulted in the exclusion of four RCTs [84-87] on low back pain, phantom limb pain, systemic lupus erythematosus, fibromyalgia and chronic pain (sample sizes ranging from 18 to 36). The exclusion of lower levels of evidence may have also resulted in the omission of other pain conditions that could be relevant targets for aVNS therapy. It is possible that rare safety events may have been missed with this strategy, although this is unlikely to be a major concern given the relatively minor side effects related to the use of aVNS. Limiting studies according to sample size, which was based on power calculations from published RCTs on aVNS [54-56], does not appear to have excluded any studies that would have affected the outcomes of this assessment. A further potential limitation is the exclusion of studies due to insufficient or missing information on which auricular nerve was stimulated, which led to the elimination of five studies on acute postoperative pain [88-92] and three on chronic pain-related conditions (rheumatoid arthritis [93], chemoradiotherapy pain [94] and irritable bowel syndrome [95]).

keine Suche nach grauer Literatur und Beschränkung auf deutsch- und englischsprachige Publikationen

Although a comprehensive search of medical literature databases was conducted, an extensive grey literature search was not undertaken. In addition, some relevant articles may have been overlooked by restricting the searches to studies published in the English or German language. However, clinical trial databases were searched, the references of all retrieved studies (including systematic and narrative reviews) were hand searched and some device manufacturers were contacted for additional information, so it is unlikely that any significantly sized RCTs were missed.

One preprint randomised double-blind RCT [96] was excluded because it had not undergone peer review at the time of writing. This trial compared percutaneous aVNS with sham treatment in 53 patients undergoing abdominal surgery for cancer and demonstrated a reduction in opioid use in the subgroup of patients who had an open surgical procedure, although there were no differences in pain levels. An additional RCT [97] was not available at the time of writing. This study measured the effects of aVNS or standard care on postoperative ileus in 134 patients undergoing laparoscopic radical resection of colorectal cancer, although it is unclear whether pain outcomes were also measured.

1 RCT wegen fehlendem peer-review ausgeschlossen und 1 RCT war nicht erhältlich

6.4 Conclusion

The limited evidence indicates that transcutaneous aVNS may be a safe and effective adjunctive treatment for reducing rebound pain after femoral nerve block in patients undergoing anterior cruciate ligament reconstruction, and for reducing pain in patients with myofascial pain syndrome and episodic migraine without aura.

aVNS: sichere und wirksame Zusatztherapie bei Rebound-Schmerzen nach ACL-Rekonstruktion…

The limited evidence also suggests that percutaneous aVNS is a safe and effective adjunctive therapy for reducing pain and improving symptoms in pain-related gastrointestinal disorders, particularly irritable bowel syndrome.

…und einigen chronischen Schmerzen

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations for acute postoperative and chronic pain

	The inclusion in the catalogue of benefits is **recommended**.
X	The inclusion in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is **currently not recommended**.
	The inclusion in the catalogue of benefits is **not recommended**.

Reasoning:

Population One: Acute postoperative pain

aVNS: sichere und wirksame Zusatztherapie bei Rebound-Schmerzen nach ACL-Rekonstruktion, jedoch nicht auf andere postoperative Schmerzen übertragbar

1 laufendes RCT

Reducing postoperative pain is important, not only for patient comfort and expediting recovery, but also for avoiding the development of CPSP. High certainty evidence from one RCT indicated that transcutaneous aVNS was superior to sham (both in addition to standard care) in reducing rebound pain after femoral nerve block, analgesia consumption, rescue medication usage and sleep disturbance during the first twelve hours after knee reconstruction surgery. Limited low certainty evidence does not support the use of aVNS for other type of acute postoperative pain. One large ongoing trial assessing aVNS versus sham treatment for the relief of pain in 600 patients undergoing arthroplasty in China is due for completion in July 2024, but the results from this may not be generalisable to other operative procedures. Based on this, a re-evaluation is recommended not before 2025.

Population Two: Chronic pain

aVNS: sichere und wirksame Zusatztherapie bei gastrointestinalen Erkrankungen bei 11 – 18-jährigen &

mögliche positive Effekte bei Migräne und myofaszialem Schmerzsyndrom

11 laufende RCTs

High certainty evidence from one RCT indicates that adjunctive percutaneous aVNS is more effective and as safe as adjunctive sham treatment in youth aged 11 to 18 years with pain-related gastrointestinal disorders, particularly irritable bowel syndrome. Lower certainty evidence from one RCT indicated that this may also be true for adults (18 to 75 years of age). There are currently no ongoing RCTs of aVNS for gastrointestinal disorders.

Adjunctive transcutaneous aVNS may also reduce pain in patients with episodic migraine without aura or myofascial pain syndrome, but the results should be interpreted with caution owing to the lower certainty of evidence for these indications.

Of the 11 ongoing RCTs identified, six are evaluating the use of aVNS in various chronic musculoskeletal conditions. There are currently no ongoing RCTs of aVNS for chronic migraine or other headaches. Based on this, the re-evaluation is recommended not before 2024.

Empfehlung: Aufnahme nur für ausgewählte Patient*innen

Based on the available evidence the inclusion of aVNS in the hospital benefit catalogue should be limited to selected patients.

8 References

[1] Raja S. N., Carr D. B., Cohen M., Finnerup N. B., Flor H., Gibson S., et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982.

[2] Cohen S. P., Vase L. and Hooten W. M. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-2097.

[3] Bonezzi C., Fornasari D., Cricelli C., Magni A., Ventriglia G. Not all pain is created equal: Basic definitions and diagnostic work-up. Pain and Therapy. 2020;9(Suppl 1):1-15.

[4] Fitzcharles M. A., Cohen S. P., Clauw D. J., Littlejohn G., Usui C., Hauser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397(10289):2098-2110.

[5] International Association for the Study of Pain (IASP). Terminology. 2011 [cited 07.02.2023]. Available from: https://www.iasp-pain.org/resources/terminology/.

[6] Treede R. D., Rief W., Barke A., Aziz Q., Bennett M. I., Benoliel R., et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-1007.

[7] World Health Organization (WHO). International Classification of Diseases, Eleventh Revision (ICD-11). 2019 [cited07.02.2023]. Available from: https://icd.who.int/.

[8] Mills S. E. E., Nicolson K. P., Smith B. H. Chronic pain: a review of its epidemiology and associated factors in population-based studies. British Journal of Anaesthia. 2019;123(2):e273-e283.

[9] Wylde V., Dennis J., Beswick A. D., Bruce J., Eccleston C., Howells N., et al. Systematic review of management of chronic pain after surgery. British Journal of Surguery. 2017;104(10):1293-1306.

[10] Kehlet H., Jensen T. S., Woolf C. J. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-1625.

[11] Macrae W. A. Chronic post-surgical pain: 10 years on. British Journal of Anaesthia. 2008;101(1):77-86.

[12] Statistik Austria. Austrian Health Interview Survey 2019. 2020 [cited 07.02.2023]. Available from: https://www.statistik.at/en/statistics/population-and-society/health/health-status/self-perceived-health.

[13] McGreevy K., Bottros M. M., Raja S. N. Preventing chronic pain following acute pain: Risk factors, preventive strategies, and their efficacy. European Journal of Pain Supplements 2011;5(2):365-372.

[14] Gerbershagen H. J., Pogatzki-Zahn E., Aduckathil S., Peelen L. M., Kappen T. H., van Wijck A. J., et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. Anesthesiology. 2014;120(5):1237-1245.

[15] Reddi D., Curran N. Chronic pain after surgery: pathophysiology, risk factors and prevention. Postgraduate Medical Journal 2014;90(1062):222-227; quiz 226.

[16] Chou R., Gordon D. B., de Leon-Casasola O. A., Rosenberg J. M., Bickler S., Brennan T., et al. Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. Journal of Pain. 2016;17(2):131-157.

[17] Henschke N., Kamper S. J., Maher C. G. The epidemiology and economic consequences of pain. Mayo Clinic Proceedings. 2015;90(1):139-147.

[18] Gobina I., Villberg J., Valimaa R., Tynjala J., Whitehead R., Cosma A., et al. Prevalence of self-reported chronic pain among adolescents: Evidence from 42 countries and regions. European Journal of Pain. 2019;23(2):316-326.

[19] Juniper M., Le T. K., Mladsi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. Expert Opinion on Pharmacotherapy. 2009;10(16):2581-2592.

[20] Reid K. J., Harker J., Bala M. M., Truyers C., Kellen E., Bekkering G. E., et al. Epidemiology of chronic non-cancer pain in Europe: Narrative review of prevalence, pain treatments and pain impact. Current Medical Research and Opinion. 2011;27(2):449-462.

[21] Lucas J., van Doorn P., Hegedus E., Lewis J., van der Windt D. A systematic review of the global prevalence and incidence of shoulder pain. BMC Musculoskeletal Disorders. 2022;23(1):1073.

[22] Peat G., McCarney R., Croft P. Knee pain and osteoarthritis in older adults: A review of community burden and current use of primary health care. Annals of Rheumatic Diseases. 2001;60(2):91-97.

[23] Jaksch W., Likar R., Folkes E., Machold K., Herbst F., Pils K., et al. [Quality assurance of pain care in Austria: Classification of management facilities]. Wiener Medizinische Wochenschrift. 2017;167(15-16):349-358.

[24] Vos T., Flaxman A. D., Naghavi M., Lozano R., Michaud C., Ezzati M., et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163-2196.

[25] Murray C. J., Vos T., Lozano R., Naghavi M., Flaxman A. D., Michaud C., et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-2223.

[26] Krahulec E., Schmidt L. J., Habacher W., Kratzer H. [Chronic pain. Overview of out-patient pain treatment in Austria]. Schmerz. 2012;26(6):715-720.

[27] International Association for the Study of Pain (IASP). Pain treatment services. 2021 [cited 07.02.2023]. Available from: https://www.iasp-pain.org/resources/guidelines/pain-treatment-services/.

[28] Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V. (DGAI). S3-Leitlinie behandlung akuter perioperativer und posttraumatischer schmerzen. DGAI, 2021 [cited 20.02.2023]. Available from: https://register.awmf.org/de/leitlinien/detail/001-025.

[29] National Institute for Health and Care Excellence (NICE). Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. NICE, 2021 [cited 20.02.2023]. Available from: https://www.nice.org.uk/guidance/ng193/resources/chronic-pain-primary-and-secondary-in-over-16s-assessment-of-all-chronic-pain-and-management-of-chronic-primary-pain-pdf-66142080468421.

[30] National Institute for Health and Care Excellence (NICE). Chronic pain (primary and secondary) – using NICE guidelines for assessment and management. NICE, 2021 [cited 20.02.2023]. Available from: https://www.nice.org.uk/guidance/ng193/resources/visual-summary-pdf-9073473517.

[31] Becker A, Becker M., Engeser P. S1-Leitlinie chronischer schmerz. AWMF, 2013 [cited 20 February 2023]. Available from: https://register.awmf.org/de/leitlinien/detail/053-036.

[32] Chakravarthy K., Chaudhry H., Williams K., Christo P. J. Review of the uses of vagal nerve stimulation in chronic pain management. Current Pain and Headache Reports. 2015;19(12):54.

[33] Yuan H., Silberstein S. D. Vagus Nerve and vagus nerve stimulation, a comprehensive review: Part I. Headache. 2016;56(1):71-78.

[34] Johnson R. L., Wilson C. G. A review of vagus nerve stimulation as a therapeutic intervention. Journal of Inflammation Research. 2018;11:203-213.

[35] Kaniusas E., Kampusch S., Tittgemeyer M., Panetsos F., Gines R. F., Papa M., et al. Current directions in the auricular vagus nerve stimulation I - A Physiological perspective. Frontiers in Neuroscience. 2019;13:854.

[36] De Couck M., Nijs J. and Gidron Y. You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. Clinical Journal of Pain. 2014;30(12):1099-1105.

[37] Kaniusas E., Kampusch S., Tittgemeyer M., Panetsos F., Gines R. F., Papa M., et al. Current Directions in the Auricular Vagus Nerve Stimulation II - An Engineering Perspective. Frontiers in Neuroscience. 2019;13:772.

[38] Verma N., Mudge J. D., Kasole M., Chen R. C., Blanz S. L., Trevathan J. K., et al. Auricular vagus neuromodulation-A systematic review on quality of evidence and clinical effects. Frontiers in Neuroscience. 2021;15:664740.

[39] Redgrave J., Day D., Leung H., Laud P. J., Ali A., Lindert R., et al. Safety and tolerability of transcutaneous vagus nerve stimulation in humans; A systematic review. Brain Stimulation. 2018;11(6):1225-1238.

[40] Mertens A., Gadeyne S., Lescrauwaet E., Carrette E., Meurs A., De Herdt V., et al. The potential of invasive and non-invasive vagus nerve stimulation to improve verbal memory performance in epilepsy patients. Scientific Reports. 2022;12(1):1984.

[41] Gonzalez H. F. J., Yengo-Kahn A., Englot D. J. Vagus nerve stimulation for the treatment of epilepsy. Neurosurgery Clinics of North America. 2019;30(2):219-230.

[42] Panebianco M., Rigby A., Weston J., Marson A. G. Vagus nerve stimulation for partial seizures. Cochrane Database of Systematic Reviews. 2015;2015(4):CD002896.

[43] Revesz D., Rydenhag B., Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. Journal of Neurosurgery Pediatrics. 2016;18(1):97-104.

[44] Yap J. Y. Y., Keatch C., Lambert E., Woods W., Stoddart P. R., Kameneva T. Critical review of transcutaneous vagus nerve stimulation: Challenges for translation to clinical practice. Frontiers in Neuroscience. 2020;14:284.

[45] de Gurtubay I. G., Bermejo P., Lopez M., Larraya I., Librero J. Evaluation of different vagus nerve stimulation anatomical targets in the ear by vagus evoked potential responses. Brain Behavior. 2021;11(11):e2343.

[46] Mercante B., Ginatempo F., Manca A., Melis F., Enrico P., Deriu F. Anatomo-physiologic basis for auricular stimulation. Medical Acupuncture. 2018;30(3):141-150.

[47] Butt M. F., Albusoda A., Farmer A. D., Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. Journal of Anatomy. 2020;236(4):588-611.

[48] Frangos E., Richards E. A., Bushnell M. C. Do the psychological effects of vagus nerve stimulation partially mediate vagal pain modulation? Neurobiology of Pain. 2017;1:37-45.

[49] Qureshi I. S., Datta-Chaudhuri T., Tracey K. J., Pavlov V. A., Chen A. C. H. Auricular neural stimulation as a new non-invasive treatment for opioid detoxification. Bioelectronic Medicine. 2020;6:7.

[50] Straube A., Ellrich J., Eren O., Blum B., Ruscheweyh R. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. Journal of Headache and Pain. 2015;16:543.

[51] Gupta A., Kaur K., Sharma S., Goyal S., Arora S., Murthy R. S. Clinical aspects of acute post-operative pain management & its assessment. Journal of Advanced Pharmaceutical Technology & Research. 2010;1(2):97-108.

[52] Treede R. D., Rief W., Barke A., Aziz Q., Bennett M. I., Benoliel R., et al. Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.

[53] Farmer A. D., Strzelczyk A., Finisguerra A., Gourine A. V., Gharabaghi A., Hasan A., et al. International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). Frontiers in Human Neuroscience. 2020;14:568051.

[54] Lim G., Nowakowski E., LaSorda K. R., Altamirano V., Morgan M., Makeen M., et al. NSS-Bridge device for post-cesarean delivery analgesia: A randomized controlled trial. Journal of Obstetrics and Gynaecology Research. 2022;5(3):210-218.

[55] Michalek-Sauberer A., Heinzl H., Sator-Katzenschlager S. M., Monov G., Knolle E., Kress H. G. Perioperative auricular electroacupuncture has no effect on pain and analgesic consumption after third molar tooth extraction. Anesthia & Analgesia. 2007;104(3):542-547.

[56] Zhou Q., Yu L., Yin C., Zhang Q., Tai Y., Zhu L., et al. Effect of transauricular vagus nerve stimulation on rebound pain after ropivacaine single injection femoral nerve block for anterior cruciate ligament reconstruction: A randomized controlled trial. Journal of Pain Research. 2022;15:1949-1958.

[57] European Network for Health Technology Assessment (EUnetHTA). The HTA Core Model® for rapid relative effectiveness assessments. Version 4.2. 2015 [cited 28.02.2023]. Available from: https://corehta.info/model/HTACoreModel_ForRapidREAs4.2.pdf.

[58] Sterne J. A. C., Savovic J., Page M. J., Elbers R. G., Blencowe N. S., Boutron I., et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

[59] Guyatt G., Oxman A. D., Sultan S., Brozek J., Glasziou P., Alonso-Coello P., et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. Journal of Clinical Epidemiology. 2013;66(2):151-157.

[60] Patel K. V., Amtmann D., Jensen M. P., Smith S. M., Veasley C., Turk D. C. Clinical outcome assessment in clinical trials of chronic pain treatments. Pain Reports. 2021;6(1):e784.

[61] Dworkin R. H., Turk D. C., Farrar J. T., Haythornthwaite J. A., Jensen M. P., Katz N. P., et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.

[62] European Network for Health Technology Assessment (EUnetHTA). Endpoints used in relative effectiveness assessment. Safety. 2015 [cited 7 February 2023]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/WP7-SG3-GL-safety_amend2015.pdf.

[63] Smith S. M., Wang A. T., Katz N. P., McDermott M. P., Burke L. B., Coplan P., et al. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTTION systematic review and recommendations. Pain. 2013;154(7):997-1008.

[64] Blank J. J., Liu Y., Yin Z., Spofford C. M., Ridolfi T. J., Ludwig K. A., et al. Impact of auricular neurostimulation in patients undergoing colorectal surgery with an enhanced recovery protocol: A pilot randomized, controlled trial. Diseases of the Colon & Rectum. 2021;64(2):225-233.

[65] Kovacic K., Hainsworth K., Sood M., Chelimsky G., Unteutsch R., Nugent M., et al. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: A randomised, double-blind, sham-controlled trial. Lancet Gastroenterology and Hepatology. 2017;2(10):727-737.

[66] Krasaelap A., Sood M. R., Li B. U. K., Unteutsch R., Yan K., Nugent M., et al. Efficacy of auricular neurostimulation in adolescents with irritable bowel syndrome in a randomized, double-blind trial. Clinical Gastroenterology and Hepatology. 2020;18(9):1987-1994 e1982.

[67] Kutlu N., Ozden A. V., Alptekin H. K., Alptekin J. O. The impact of auricular vagus nerve stimulation on pain and life quality in patients with fibromyalgia syndrome. BioMed Research International. 2020;2020:8656218.

[68] Paccione C. E., Stubhaug A., Diep L. M., Rosseland L. A., Jacobsen H. B. Meditative-based diaphragmatic breathing vs. vagus nerve stimulation in the treatment of fibromyalgia-A randomized controlled trial: Body vs. machine. Frontiers in Neurology. 2022;13:1030927.

[69] Shi X., Hu Y., Zhang B., Li W., Chen J. D., Liu F. Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. JCI Insight. 2021;6(14):22.

[70] Ünal S., Karagözoğlu Çoşkunsu D., Hatık S. H., Özden A. V. Short-term effectiveness of auricular vagus nerve stimulation in patients with myofascial pain syndrome. European Research Journal. 2022;8(5):573-582.

[71] Zhang Y., Huang Y., Li H., Yan Z., Zhang Y., Liu X., et al. Transcutaneous auricular vagus nerve stimulation (taVNS) for migraine: an fMRI study. Regional Anesthesia & Pain Medicine. 2021;46(2):145-150.

[72] Guyatt G., Oxman A. D., Akl E. A., Kunz R., Vist G., Brozek J., et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64(4):383-394.

[73] Vetter T. R., Chou R. Clinical trial design methodology for pain outcome studies. In: Benzon H. T., Rathmell J. P., Wu C. L., Turk D. C., Argoff C. E., Hurley R. W., editors. Practical Management of Pain (Fifth Edition): Elsevier Ltd, 2014.

[74] Olsen M. F., Bjerre E., Hansen M. D., Hilden J., Landler N. E., Tendal B., et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Medicine. 2017;15(1):35.

[75] Gatchel R. J., Mayer T. G., Choi Y., Chou R. Validation of a consensus-based minimal clinically important difference (MCID) threshold using an objective functional external anchor. Spine Journal. 2013;13(8):889-893.

[76] Olsen M. F., Bjerre E., Hansen M. D., Tendal B., Hilden J., Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. Journal of Clinical Epidemiology. 2018;101:87-106 e102.

[77] Zhuang C. L., Ye X. Z., Zhang X. D., Chen B. C., Yu Z. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A meta-analysis of randomized controlled trials. Diseases fo the Colon & Rectum. 2013;56(5):667-678.

[78] Gray A., Kehlet H., Bonnet F., Rawal N. Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence? British Journal of Anaesthia. 2005;94(6):710-714.

[79] Hyllested M., Jones S., Pedersen J. L., Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. British Journal of Anaesthia. 2002;88(2):199-214.

[80] Sunderland S., Yarnold C. H., Head S. J., Osborn J. A., Purssell A., Peel J. K., et al. Regional versus general anesthesia and the incidence of unplanned health care resource utilization for postoperative pain after wrist fracture surgery: Results from a retrospective quality improvement project. Regional Anesthesia & Pain Medicine. 2016;41(1):22-27.

[81] Barry G. S., Bailey J. G., Sardinha J., Brousseau P., Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. British Journal of Anaesthia. 2021;126(4):862-871.

[82] Williams B. A., Ibinson J. W., Mangione M. P., Modrak R. T., Tonarelli E. J., Rakesh H., et al. Research priorities regarding multimodal peripheral nerve blocks for postoperative analgesia and anesthesia based on hospital quality data extracted from over 1,300 cases (2011-2014). Pain Medicine. 2015;16(1):7-12.

[83] Grill W. M., Jr. Modeling the effects of electric fields on nerve fibers: influence of tissue electrical properties. IEEE Transactions on Bio-medical Engineering. 1999;46(8):918-928.

[84] Melzack R., Katz J. Auriculotherapy fails to relieve chronic pain. A controlled crossover study. JAMA. 1984;251(8):1041-1043.

[85] Woodbury A., Krishnamurthy V., Gebre M., Napadow V., Bicknese C., Liu M., et al. Feasibility of auricular field stimulation in fibromyalgia: evaluation by functional magnetic resonance imaging, randomized trial. Pain Medicine. 2021;22(3):715-726.

[86] Katz J., Melzack R. Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. Journal of Pain & Symptom Management. 1991;6(2):73-83.

[87] Aranow C., Atish-Fregoso Y., Lesser M., Mackay M., Anderson E., Chavan S., et al. Transcutaneous auricular vagus nerve stimulation reduces pain and fatigue in patients with systemic lupus erythematosus: a randomised, double-blind, sham-controlled pilot trial. Annals of Rheumatic Diseases. 2021;80(2):203-208.

[88] Chung Y. C., Tsou M. Y., Chen H. H., Lin J. G., Yeh M. L. Integrative acupoint stimulation to alleviate postoperative pain and morphine-related side effects: A sham-controlled study. International Journal of Nursing Studies. 2014;51(3):370-378.

[89] Fan Q., Lei C., Wang Y., Yu N., Wang L., Fu J., et al. Transcutaneous electrical acupoint stimulation combined with auricular acupressure reduces postoperative delirium among elderly patients following major abdominal surgery: A randomized clinical trial. Frontiers in Medicine. 2022;9:855296.

[90] Hendawy H. A., Abuelnaga M. E. Postoperative analgesic efficacy of ear acupuncture in patients undergoing abdominal hysterectomy: A randomized controlled trial. BMC Anesthesiology. 2020;20(1).

[91] Holzer A., Leitgeb U., Spacek A., Wenzl R., Herkner H., Kettner S. Auricular acupuncture for postoperative pain after gynecological surgery: A randomized controlled trail. Minerva Anestesiologica. 2011;77(3):298-304.

[92] Likar R., Jabarzadeh H., Kager I., Trampitsch E., Breschan C., Szeles J. [Electrical point stimulation (P-STIM) via ear acupuncture: A randomized, double-blind, controlled pilot study in patients undergoing laparoscopic nephrctomyX]. Schmerz. 2007;21(2):154-159.

[93] Bernateck M., Becker M., Schwake C., Hoy L., Passie T., Parlesak A., et al. Adjuvant auricular electroacupuncture and autogenic training in rheumatoid arthritis: A randomized controlled trial. Auricular acupuncture and autogenic training in rheumatoid arthritis. Forschende Komplementärmedizin. 2008;15(4):187-193.

[94] Chou Y. H., Yeh M. L., Huang T. S. and Hsu H. Acupoint stimulation improves pain and quality of life in head and neck cancer patients with chemoradiotherapy: A randomized controlled trial. Asia-Pacific Journal of Oncology Nursing. 2022;9(1):61-68.

[95] Huang Z., Lin Z., Lin C., Chu H., Zheng X., Chen B., et al. Transcutaneous electrical acustimulation improves irritable bowel syndrome with constipation by accelerating colon transit and reducing rectal sensation using autonomic mechanisms. American Journal of Gastroenterology. 2022;117(9):1491–1501.

[96] Chelly J. E., Holtzman M. P., Bartlett D. L., Choudry H. A., Pingpank J. F., Zureikat A. H., et al. Reduction in postoperative opioid requirement associated with use of the NSS-2® Bridge device, a disposable auriculo-nerve field stimulator, and factors affecting the response in cancer patients undergoing abdominal surgical procedures. medRxiv. 2022. DOI: 10.1101/2022.02.02.22270328.

[97] Ru O., Jin X., Qu L., Long D., Liu M., Cheng L., et al. Low-intensity transcutaneous auricular vagus nerve stimulation reduces postoperative ileus after laparoscopic radical resection of colorectal cancer: a randomized controlled trial. Minerva Anestesiologica. 2022;3:03.

[98] Caplan A., Walker L., Rasquin A. Development and preliminary validation of the questionnaire on pediatric gastrointestinal symptoms to assess functional gastrointestinal disorders in children and adolescents. Journal of Pediatric Gastroenterology and Nutrition. 2005;41(3):296-304..

[99] European Network for Health Technology Assessment (EUnetHTA) Joint Action 2 WP. Levels of evidence: Internal validity (of randomized controlled trials). EUnetHTA, 2013 [cited 07.02.2023]. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[100] Gracely R. H., Ceko M., Bushnell M. C. Fibromyalgia and depression. Pain Research and Treatment. 2012;2012:486590.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Acute postoperative pain: Results from randomised controlled trials

Author, year	Blank 2021 [64]	Lim 2022 [54]	Michalek-Sauberer 2007 [55]	Zhou 2022 [56]
Country	USA	USA	Austria	China
Sponsor	None Neurostimulation devices were provided by the manufacturer free of charge.	National Institutes of Health University of Pittsburgh School of Medicine	Biegler Medizinelektronik GmbH (Mauerbach, Austria) supplied the P-Stim devices and acetaminophen medication	Innovation guide Project Science and Technology Winter Olympics special project grant and Hebei provincial government
Conflict of interest	None declared	None declared	None declared	None declared
Study design	Prospective, double blind, multicentre	Prospective, double blind, single centre	Prospective, double blind, single centre	Prospective, double blind, single centre
Duration	December 2016 to March 2018	August 2020 to June/2021	October 2002 to June 2004	January 2022 to March 2022
Intervention	Percutaneous aVNS	Percutaneous aVNS	Percutaneous aVNS	Transcutaneous aVNS
Device	BRIDGE (Innovative Health Solutions, LLC, Indiana, USA)	BRIDGE (Innovative Health Solutions, LLC, Indiana, USA)	P-Stim device (Biegler Medizinelektronik GmbH, Mauerbach, Austria)	TENS 7000 (Roscoe Medical, Ohio, USA)
Stimulation parameters	NR	NR	3 s pulses (3 hours on, 3 hours off), 2-100 Hz	300 µs pulses (1 hour on, 1 hour off), 30 Hz
Electrode location	Temporal process of the zygomatic bone, the antihelix, and the posterolateral auricle	Temporal process of the zygomatic bone, the antihelix, and the posterolateral auricle	Auricular acupoints; 1 (tooth), 55 (Shen Men), and 84 (mouth, which is located in the concha)	Cymba concha
Treatment duration	5 days after surgery	5 days after surgery	48 hours after surgery	12 hours after surgery
Comparator	Sham (identical to active device but without electical charge)	C1: Sham (identical to active device but with smooth electrodes and no electical charge) C2: Standard care	C1: Sham (identical to active device but without electical charge) C2: Sham (identical to active device but with smooth electrodes and no electical charge)	Sham (electrical stimulation at the earlobe and tail of the helix on the left ear)
Adjunctive treatments	Intravenous hydromorphone, transitioned to oxycodone when appropriate, and oral acetaminophen as needed. Nonsteroidal anti-inflammatory drugs and other pharmacological analgesics with heterogenous clinical use were not permitted during the study period.	Intravenous ketorolac for 24 hours, followed by conversion to ibuprofen and acetaminophen. Oral oxycodone was given for pain rated 7 or higher (scale 0-10), or for any intolerable pain.	Acetaminophen (maximum 3 g daily). Mefenamic acid permitted as rescue medication (maximum 1,500 mg daily).	Intravenous patient-controlled anaesthesia with sufentanil and ondansetron hydrochloride as needed. Rescue medication of ketorolac (up to 90 mg/day) and tramadol (up to 200 mg/day).

Author, year	Blank 2021 [64]	Lim 2022 [54]	Michalek-Sauberer 2007 [55]	Zhou 2022 [56]
Number of pts **I vs. C**	28 vs. 24	21 vs. 25 vs. 20	76 vs. 37 vs. 36	39 vs. 39
Operative procedure	Laparoscopic or open small- or large bowel resection with or without ostomy	Scheduled Cesarean delivery	Elective extraction of one impacted mandibular third molar	Anterior cruciate ligament reconstruction
Inclusion criteria	English-speaking adults who were able to independently consent; scheduled to undergo laparoscopic or open small- or large-bowel resection with or without ostomy	Healthy pregnant women 18 years or older with a singleton; planned Cesarean delivery under neuraxial anaesthesia	Adults aged 18 to 35 years scheduled for elective extraction of one impacted mandibular third molar; ASA physical status I–II [a]	Adults aged 18 to 65 years undergoing anterior cruciate ligament reconstruction; ASA physical status I–III [a]
Exclusion criteria	History of chronic pain disorder; active opiate abuse; need for emergent procedure; unplanned admission to the intensive care unit; prolonged intubation Device-specific exclusion criteria: History of seizures; cerebrovascular accidents or aneurysms; active pregnancy; recent organ transplant; myocardial infarction within 6 months of the study; fully therapeutic anticoagulation; coagulopathy; implanted on-demand devices; skin rash or infection around ear; severe adhesive tape allergy	Not fluent in English; unable to participate in informed consent discussions, or unable to give informed consent for any reason; unable to participate fully in all study procedures for any reason; Cesarean delivery under general anesthesia; history of hemophilia; pacemakers or implantable electronic devices; history of psoriasis or other skink conditions precluding device application; needed a rescue abdominal block; Cesaran delivery with unanticipated additional procedures	Previous experience with acupuncture; language difficulties; history of drug abuse; chronic pain therapy; lesions at the external ear; immunosuppression; presence of a pacemaker; asthma; coagulation disorders; neurological or psychiatric disorders; pregnancy; allergy to acetaminophen or mefenamic acid	Body mass index >35 kg/m2; allergy to local anesthetics; severe cardiopulmonary disease; any chronic pain; systemic steroid and chronic opioid use; psychiatric disorders; communication issues; inability to use a patient-controlled analgesia pump; failed femoral nerve block (no sensory block or NRS score >3 in postanesthesia care unit)
Age of patients (yrs), mean [SD], median (range) **I vs. C**	56.0 [11.5] vs. 61.5 [11.5]	32.7 [5.5] vs. 31.4 [5.8] vs. 32.1 [4.7]	27 (18-35) vs. 24 (20-35) vs. 26 (19-35)	32 [8.9] vs. 33.7 [10.5]
Sex, male n (%)	14 (50) vs. 15 (63)	0	27 (36) vs. 24 (65) vs. 20 (56)	22 (56.4) vs. 19 (48.7)
Length of follow-up	Days 1-5 of treatment; 2 weeks and 30 days after start of treatment	Days 1-5 of treatment	48 hours after start of treatment	48 hours after start of treatment
Losses to follow-up, n (%)	None	1 (5) vs. 5 (20) vs. 1 (5)	8 (12) vs. 3 (8) vs. 3 (8)	None
Differences in baseline demographics between groups	None	None	The electroacupuncture group had more women (p=0.008) and smokers (p=0.047).	None

Author, year	Blank 2021 [64]	Lim 2022 [54]	Michalek-Sauberer 2007 [55]	Zhou 2022 [56]
Outcomes				
Efficacy				
Pain scores, mean [SD]	**Day 5** **I [n=28] vs. C [n=24]:** No significant differences in daily NRS scores, except for day 3: 3.9 vs. 2.7; **p=0.03**	**I [n=20] vs. C1 [n=20] vs. C2 [n=20]:** 72 hours: Pain with movement (VAS): 4.6 [2.3] vs. 4.6 [2.5] vs. 4.2 [2.3] Pain at rest and with movement were similar between treatment groups across days 1 through 5.	**I [n=63] vs. C1 [n=33] vs. C2 [n=28]:** **Percieved pain reduction** 48 hours, n (%): 31 (49) vs. 12 (36) vs. 11 (39) Median fraction of time pain >2 on a 5-point scale: 33% vs. 22% vs. 30% (no signficant difference between groups)	**I [n=39] vs. C [n=39]** No significant differences were observed between the two groups, except at 8 and 12 hours after surgery when NRS scores were significantly lower in the active than the sham group (p<0.05) **Rebound pain** 12 hours, n (%): 7 (18) vs. 16 (41); **p=0.03** **Duration of rebound pain (hours)** 12 hours, mean [SD]: 1.7 [0.6] vs. 2.4 [0.5]; **p=0.002**
Analgesia consumption, mean [SD] (range)	**I [n=28] vs C [n=24]:** **Inpatient opioid use (MME/day)** Days 1-5: 90.8 [54.93] vs. 90.3 [43.0]; p=0.97 **Opioid use n (%)** 2 weeks: 2 (7) vs. 3 (1); p=0.56 30 days: 1 (4) vs 0; p=0.37	**I [n=20] vs. C1 [n=20] vs. C2 [n=20]:** **Opioid consumption (MME)** Days 1-5: 51.1 [56.6] vs. 71.6 [90.3] vs. 42.8 [44.0]	**I [n=60] vs. C1 [n=31] vs. C2 [n=27]:** **Acetaminophen tablets required:** 48 hours: 5.2 (0-12) vs 4.7 (0-11) vs 5.4 (0-10) (no significant difference between groups)	**I [n=39] vs. C [n=39]** **No. of times to press the analgesia pump, median (IQR):** 0-12 hours: 2 (0-2) vs. 3 (0.5-4); p=0.02 12-24 hours: 2 (0-3) vs. 2 (1-3); p=0.95 24-48 hours: 2(1.25-3) vs. 2 (2-3); p=0.73
Readmission rates, n (%)	**I [n=28] vs C [n=24]:** 30 days: 2 (7) vs. 1 (4); p=0.65	NR	NR	NR
Length of hospitalisation (days), mean [SD]	4.7 [1.8] vs. 5.5 [5.2]; p=0.66	NR	NR	NR

Author, year	Blank 2021 [64]	Lim 2022 [54]	Michalek-Sauberer 2007 [55]	Zhou 2022 [56]
Use of rescue medication, n (%)	NR	**I [n=20] vs. C1 [n=20] vs. C2 [n=20]:** **Opioid-free hospitalisation, n (%)** Days 1-5: 8 (40) vs. 4 (20) vs. 6 (30)	**I [n=63] vs. C1 [n=34] vs. C2 [n=32]:** **Mefenamic acid additional use:** 48 hours, n (%): 12 (19) vs 6 (18) vs 6 (19) (no significant difference between groups)	**I [n=39] vs. C [n=39]** Patients requiring additional analgesics, n (%): 0-12 hours: 10 (26) vs. 20 (51); p=0.004 12-24 hours: 9 (23) vs. 8 (21); p=0.8 24-48 hours: 5 (13) vs. 4 (10); p=0.4
Postoperative nausea and vomiting n (%)	No significant difference between groups for nausea	NR	NR	**I [n=39] vs. C [n=39]** 48 hours, n (%): 10 (26) vs. 13 (33%); p=0.46
Patient satisfaction	Participants were satisfied with the device: 8.2 [SD 2.6] (scale 0-10); sample size was not reported	NR	NR	NR
Safety				
Procedure-related adverse events, n (%)	**I [n=28] vs. C [n=24]:** Days 1-5: None	**I [n=20] vs. C1 [n=20] vs. C2 [n=20]:** Days 1-5: 1 patient in the active treatment group withdrew due to device discomfort	**I [n=63] vs. C1 [n=33] vs. C2 [n=27]:** 48 hours, n (%): Tiredness: 10 (16) vs 6 (18) vs 4 (15) Pain at the ear: 7 (11) vs 4 (12) vs 2 (7)	**I [n=39] vs. C [n=39]** 48 hours, n (%): Pruritus: 0 vs. 1 (3%) Sleep disturbance: 12 (31) vs. 21 (54); **p=0.03** Light-headedness: None Ear irritation: None Tinnitus: None
Procedure-related serious adverse events, n (%)	**I [n=28] vs. C [n=24]:** Days 1-5: None	NR	NR	NR
Device tolerability, n (%)	NR	Mean (0-100 scale) in active treatment group (n=20) ranged from 76.5 to 86.2 over Days 0-3	**I [n=63] vs. C1 [n=34] vs. C2 [n=29]:** Proportion of patients rating treatment comfort as moderate to good: 59 (94) vs. 31 (91) vs. 26 (90)	NR

Abbreviations: *ASA – American Society of Anesthesiologists; aVNS – auricular vagus nerve stimulation; IQR – interquartile range; MME – milligram morphine equivalent; NR – not reported; NRS – numeric rating scale; SD – standard deviation; VAS – visual analogue scale*

[a] *ASA I – a normal healthy patient; ASA II – a patient with mild systemic disease; ASA III – a patient with a severe systemic disease that is not life-threatening.*

Table A-2: Chronic pain conditions: Results from randomised controlled trials

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Country	USA	China	Turkey	Norway	China	Turkey
Sponsor	American Neurogastro-enterology and Motility Society	National Natural Science Foundation of China	Not reported	South-East Regional Health Authority, Norway	Medical Scientific Research Foundation of Guangdong Province, China and the Administration of Traditional Chinese Medicine of Guangdong Province, China	None
Conflict of interest	None declared	None declared	None declared	None declared	None declared	None declared
Study design	Prospective, double blind, single centre	Prospective, single blind (patients), single centre	Prospective, open label, single centre	Prospective, double blind, single centre	Prospective, double blind, single centre	Prospective, open label, single centre
Study period	June 2015 to November 2016	Not reported	Not reported	March 2019 to October 2020	May 2017 to May 2019	June 2018 to April 2019
Intervention (I)	Percutaneous aVNS	Transcutaneous aVNS	Transcutaneous aVNS plus a home-based exercise program	Transcutaneous aVNS	Transcutaneous aVNS	Transcutaneous aVNS plus trigger point ischemic compression and stretching exercises
Device	Neuro-Stim (Innovative Health Solutions, Indiana, USA)	SNM-FDC01 (Ningbo David Medical Device Co., Ltd, Ningbo, China)	Transcutaneous electrical nerve stimulation device Type not reported	NEMOS, (Cerbomed GmbH, Erlangen, Germany)	Electronic acupuncture treatment instrument (SDZII, Huatuo, Suzhou, China)	Vagustim (Vagustim, California, USA)
Stimulation parameters	1 ms pulses every 2 s (2 hours on, 2 hours off), 3.2 V, 1 and 10 Hz	0.5 ms pulses (2 s on, 3 s off), 0-2 mA, 25 Hz	0.5 ms pulses for 30 minutes, 10 Hz	0.25 ms pulses (30 s on, 30 s off) for 15 minutes, 0.1-10 mA, 25 Hz	0.2 ms pulses for 30 minutes, 1.5-5 mA, 1 Hz	0.5 ms pulses for 30 minutes, 10 Hz
Electrode location	Dorsal and ventral aspects of the ear near the branches of the vagal, trigeminal, facial, and glossopharyngeal nerves	Bilateral auricular concha	Inner and rear surfaces of the tragus and concha for both ears	Concha of the left ear	Left cymba concha	Tragus and concha of both ears
Treatment duration	5 days per week for 4 weeks	Twice per day for 4 weeks	Stimulation: 5 days per week for 4 weeks Exercises: 2 sets per day, 5 days per week plus weekly face-to-face sessions	Twice per day for 2 weeks	12 treatments over 4 weeks	10 sessions over 5 days

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Comparator (C)	Sham (identical to active device but without electical charge)	Sham (electrical stimulation at the elbows)	Exercises: 2 sets per day, 5 days per week plus weekly face-to-face sessions	Sham (electrical stimulation at centre of the left earlobe)[c]	Sham (electrical stimulation of tail of the helix on left ear)	Trigger point ischemic compression and stretching exercises for 10 sessions,over 5 days
Adjunctive treatments	Dose changes were not allowed during the trial I (n=57): Tricyclic antidpressants (21%); SSRIs (21%); cyproheptadine (18%) C (n=47): Tricyclic antidpressants (21%); SSRIs (40%); cyproheptadine (11%)	Polyethylene glycol 4000 powder and pinaverium bromide tablets for intolerable bowel symptoms	Not reported	Not reported	Not reported	Not reported
Number of pts allocated **I vs. C**	57 vs.47 IBS subgroup: 27 vs.23	21 vs.21	30 vs.30	28 vs.29	34 vs. 29	30 vs.30
Condition/ Duration	Abdominal pain-related functional gastrointestinal disorders Duration not reported	Constipation-predominant irritable bowel syndrome Mean duration [SD]: I: 8.9 months [8.5] C: 13.3 months [10.9]	Fibromyalgia syndrome Duration: I: 1-8 years, 33%; ≥8 years, 37% C: 1-8 years, 28%; ≥8 years, 24%	Fibromyalgia syndrome Duration: ≥3 months	Episodic migraine without aura Duration: ≥6 months	Myofascial pain syndrome Median duration (range): I: 6 months (0.25-36) C: 5.5 months (0.5-60)
Inclusion criteria	Children aged 11 to 18 years with chronic abdominal pain who met Rome III criteria[98] for abdominal pain-related functional gastrointestinal disorders; average abdominal pain intensity ≥3 on a 10-point rating scale; abdominal pain ≥2 times per week before starting the trial	Adults aged 18 to 75 years; willing to sign a written informed consent form; met Rome III criteria[98] for constipation-predominant irritable bowel syndrome	Women aged 18 to 50 years with diagnosed fibromyalgia syndrome	Adults aged 18 to 65 years; confirmed diagnosis of chronic widespread pain, including fibromyalgia; WPI ≥ 7 and SSS score ≥ 5 or WPI of 4-6 and SSS score ≥ 9; generalised pain (pain ≥4/5 regions, not including jaw, chest, or abdominal pain); symptoms present ≥ 3 months	Adult episodic migraineurs without aura aged 18 to 45 years old; right-handed; ≥6 months' migraine duration; ≥2 headache attacks per month; have not taken any prophylactic headache medications in the previous month; have not taken any psychoactive or vasoactive drugs in the past 3 months	Adults aged 20-60 years with myofascial pain syndrome and had at least one active trigger point palpable on the trapezius muscle and a taut band

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Exclusion criteria	Medications or health conditions known to cause abdominal pain; children with seizures, developmental delays, or any implanted electrical device; inability to speak English	History of previous abdominal surgery (other than appendectomy); presence of carcinoma; any organic diseases causing constipation or neurologic diseases; taking antidepressant agents; diabetes or a serious concomitant disease of the heart, liver, kidney; pregnancy or lactation; participating in another trial or enrolled in a trial during the past month; allergic reaction to surface electrodes	Pregnant, perimenopausal, or postmenopausal women; comorbid illnesses such as neurological deficits, diabetes, neuropathic disorders, chronic inflammation, immune deficiency, cardiac disorders; currently taking vitamin D; started a new drug in the last month or during the study; previous vasovagal syncope	Past history or presence of comorbid severe neurological or psychiatric disorders and/or neuro-degenerative disorders; pregnancy or planned pregnancy; planned surgery; receiving treatment for any type of eating disorder; head trauma; migraine; active heart or ear implants; individuals who have practiced meditation consistently (for more than 20 minutes/day) within the last 6 months	Headache caused by other diseases; headache attack within 48 hours prior to the experiment or during the experiment; pregnancy or lactation; any other chronic pain conditions; severe head deformity or intracranial lesions; SAS or SDS score >50	Cervical disc herniation, radiculopathy, or myelopathy; acute inflammatory disease; use of antispasmodic and analgesic medications; pregnancy
Age of patients (yrs), mean [SD] (range) **I vs. C**	15.3 (13.5-16.6) vs.15.6 (14.7-17.2) IBS subgroup: 15.3 (13.8-16.7) vs.15.6 (14.2-17.2)	41.5 [15.4] vs. 49.6 [15.6]	39.4 [8.3] vs, 38.6 [9.3]	48.3 [8.88] vs.45.5 [12.04]	Not available	38.1 [9.94] vs. 35.4 [10.7]
Sex, male n/N (%)	6/57 (11) vs. 4/47 (9) IBS subgroup: 3/27 (11) vs.2/23 (9)	4/21 (19) vs.6/21 (29)	0%	1/28 (4) vs. 1/29 (3)	Not available	Not reported
Length of follow-up	Weeks 1 to 3 of treatment Median 9.2 weeks (IQR 6.4-13.4) from the last week of treatment	4 weeks after start of treatment	4 weeks after start of treatment	2 weeks after start of treatment	4 weeks after start of treatment	5 days after start of treatment
Losses to follow-up, n (%)	7/57 (12) vs.4/47 (9) IBS subgroup: 1/51 (unclear from which group)	0 vs. 2/21 (10)	3/30 (10) vs.5/30 (17)	2/28 (7) vs.1/29 (3)	3/29 (10) vs.1/34 (3)	3/30 (10) vs.4/30 (13)

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Differences in baseline demographics between groups	Concurrent use of SSRIs was higher in the sham group (p not stated) IBS subgroup: None	None	The control group was slightly taller (p=0.047)	None	None	None
Differences in baseline measures between groups	None IBS subgroup: None	None	The control group had less pain and better phsyical function and social functionality on the SF-36 scale (p=0.02)	None	None	The control goup had a worse score on the gastrointestinal subscale of the Compass-31 scale (p=0.03) and better scores on the energy/vitality (p=0.03) and mental health (p=0.004) subscales of the SF-36
Outcomes						
Efficacy						
Pain score	**Least squares mean estimate PFSD score: I [n=57] vs. C [n=47]** Week 1: 5.75 (95% CI 1.00-10.49); **p=0.02** Week 2: 6.41 (95% CI 1.60-11.23); **p=0.009** Week 3: 11.48 (95% CI 6.63-16.32); **p<0.0001** Median 9.2 weeks' FU: Median ↓8.4 vs 0; **p=0.02** **IBS subgroup I [n=27] vs. C [n=23]:** Week 1: 7.91 (95% CI -0.004-15.82); **p=0.05** Week 2: 8.07 (95% CI 0.09-16.04); **p=0.048** Week 3: 11.53 (95% CI 3.62-19.44); **p=0.005**	**Week 4 I [n=21] vs. C [n=19]:** 4-week group difference: Mean change in VAS scores: -3.1 (SD 2.2) vs, -1.1 (SD 1.1); **p=0.001** Change in mean VAS: ↓69% vs ↓18% **(p<0.001)**	**Week 4 I [n=27] vs. C [n=25] (SD):** Mean VAS: 2.56 (1.91) vs. 3.45 (1.73); p=0.08	**Week 2 I [n=28] vs. C [n=29]:** Mean change in NRS in the last week: -0.57 (95% CI -0.83, -0.31) vs. -0.86 (95% CI -1.11, -0.61); p-value not reported for this comparison Mean change in current NRS: -0.82 (95% CI -1.32, -0.31) vs. -0.86 (95% CI -1.36, -0.36); p-value not reported for this comparison Mean change in current WPI (0-19): Week 2: -1.50 (95% CI -2.23, -0.77) vs. -1.69 (95% CI -2.39, -0.98); p-value not reported for this comparison	**Week 4 I [n=33] vs. C [n=26]:** Change in mean VAS compared with baseline: -17.4 (95% CI -25.2, -9.7) vs.-4.1 (95% CI -9.4, 1.3); **p=0.008**	**Day 5 I [n=27] vs. C [n=26]:** Mean change in VAS: -2.77 vs -1.96; **p<0.001**

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Reduction in pain ≥30% from baseline, n (%)	**Week 3** **I [n=48] vs. C [n=45]:** 28 (58) vs 13 (29); **p=0.007**	**Week 4** **I [n=21] vs C [n=19]:** 20 (95) vs 7 (37); **p<0.001** Responders:[a] 17 (81) vs 5 (26); **p=0.001**	NR	NR	NR	NR
Change in worst pain score	**Least squares mean estimate PFSD score:** **I [n=57] vs. C [n=47]:** Week 1: 1.09 (95% CI 0.34-1.85); **p=0.005** Week 2: 1.21 (95% CI 0.43-1.98); **p=0.002** Week 3: 2.15 (95% CI 1.37-2.93); **p<0.0001** Median 9.2 weeks' FU: Median ↓1.0 vs 0; **p=0.02** **IBS subgroup** **I [n=27] vs. C [n=23]:** Week 1: 1.47 (95% CI 0.22-2.71); **p=0.02** Week 2: 1.09 (95% CI -0.17-2.35); **p=0.09** Week 3: 2.38 (95% CI 1.13-3.63); **p=0.0002**	NR	NR	NR	NR	NR

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Reduction in worst pain ≥30% from baseline, n (%)	**I [n=48] vs. C [n=45]:** Week 3: 29 (60) vs. 10 (22) ; **p=0.0003** **IBS subgroup (I [n=27] vs. C [n=23]):** Week 3: 59% vs. 26%; **p=0.02** Median 9.2 weeks' FU: No difference between groups	NR	NR	NR	NR	NR
Functioning	**Median 9.2 weeks' FU** **I [n=57] vs. C [n=47]:** Mean change in FDI score: 36% vs. 0%; p-value NR	NR	NR	NR	NR	**Day 5** **I [n=27] vs C [n=26]:** Mean change in grip strenght (kg): 2.1 vs 0.5; **p=0.001**
Symptom severity	**Week 3** **I [n=57] vs. C [n=47]:** Median SRS score: 3 (IQR 1.0-4.8) vs. 1 (IQR 0.0-2.3); **p=0.0003** Pts with SRS score ≥2: 73% (n=52) vs. 35% (n=46); **p=0.0002** Effects did not remain at extended FU **IBS subgroup** **I [n=27] vs. C [n=23]:** **Median 9.2 weeks' FU:** Median change in FDI score: -4 vs. -1.5; p=0.8 **Week 3:** Median change in SRS score: 3 (IQR 2-4) vs. 0 (IQR 0-2); **p=0.003** Pts with SRS score ≥2: 78% vs. 39%; **p=0.009** Pts with SRS score ≥3: 67% vs. 22%; **p=0.002** Pts with overall symptom improvement: 81% vs. 26%; **p≤0.001**	**Week 4** **I [n=21] vs C [n=19]:** Mean IBS-SSS score: 197.1 (SD 39.6) vs. 289.5 (SD 94.4]; **p=0.001** Change in mean IBS-SSS score compared with baseline: I: 197.1 vs. 284.8; **p<0.001** C: 289.5 vs 287.6	**Week 4** **I [n=27] vs C [n=25]:** Mean FIQ score: 37.27 (SD 19.48) vs. 41.93 (SD 18.15), **p=0.4**	**Week 2** **I [n=28] vs C [n=29]:** Mean change in fibromyalgia severity[b] (0-31): -2.82 (95% CI -3.83, -1.81) vs. -2.90 (95% CI -3.89, -1.91); p-value not reported for this comparison Mean change in SSS score (0-12): -1.32 (95% CI -1.91, -0.74) vs. -1.21; p-value not reported for this comparison	**Week 4** **I [n=26] vs C [n=33]:** Change in mean migraine days: -2.5 (95% CI -3.3, --1.6) vs. -0.7 (95% CI -2.1, 0.6); **p=0.02** Change in mean migraine duration (time unit not specified): -1.5 (95% CI -2.3, -0.6) vs. 0.4 (95% CI -0.9, 1.7); **p=0.02**	**Day 5** **I [n=27] vs C [n=26]:** Mean change in Compass-31 score: Statistically significant change in favor of the intervention for the secretomotor subscale **(p=0.01)** only

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Quality of life	NR	**Week 4** **I [n=21] vs C [n=19]:** Mean IBS-QOL score: 83.2 (SD 12.5) vs. 69.5 (SD 21.2); **p=0.02** Change in mean IBS-QOL score compared with baseline: I: 83.2 vs. 69.7; **p<0.001** C: 69.5 vs. 72.6	**Week 4** **I [n=27] vs C [n=25]:** Change in mean SF-36 score: Statistically significant improvement in all 8 subscales for both groups, but between group differences were not statistically significant	NR	**Week 4** **I [n=33] vs. C [n=26]:** Change in mean MSQ score compared with baseline: 13.6 (95% CI 9.1, 18.2) vs. 11.4 (95% CI 7.0, 15.8) p=0.48	**Day 5** **I [n=27] vs C [n=26]:** Mean change in SF-36 score: No statistically significant between group differences in any of the 8 subscales
Anxiety	**Median 9.2 weeks' FU I [n=57] vs C [n=47]:** Change in median STAI-C score: -2.0 vs. 1.0; p=0.9 **IBS subgroup (I [n=27] vs. C [n=23]): Median 9.2 weeks' FU:** Median change in STAI-C score: 0 in both groups	**Week 4** **I [n=21] vs C [n=19]:** Mean SAS score: 38.7 (SD 5.6) vs. 47.9 (SD 9.0); **p<0.001** Change in mean SAS score compared with baseline: I: 38.7 vs. 45.0; **p<0.001** C: 47.9 vs.49.4	**Week 4** **I [n=27] vs C [n=25]:** Mean change in BAS score: 13.00 (IQR 13.00) vs. 13.00 (IQR 11.00) vs.; p=0.6	NR	**Week 4** **I [n=33] vs. C [n=26]:** Change in mean SAS score compared with baseline: -3.0 (95% CI -4.5, --1.6) vs. -2.7 (95% CI -4.7, -0.7); p=0.77	NR
Depression	NR	**Week 4** **I [n=21] vs C [n=19]:** Mean SDS score: 42.6 (SD 8.1) vs. 50.7 (SD 11.1); **p=0.01** Change in mean SAS score compared with baseline: I: 42.6 vs.. 47.5; **p<0.001** C: 50.7 vs. 52.0	**Week 4** **I [n=27] vs C [n=25]:** Mean change in BDS score: 8.00 (IQR 12.00) vs. 13.00 (IQR 12.00); p=0.2	NR	**Week 4** **I [n=33] vs. C [n=26]:** Change in mean SDS score compared with baseline: -2.9 (95% CI -4.5, --1.4) vs. -1.0 (95% CI -4.0, 2.1); p=0.2	NR
Proportion of patients satisfied with treatment	**6-12 months' FU** **I [n=43] vs C [n=30]:** 79% vs. 40%; **p=0.007**	NR	NR	NR	NR	NR

Author, year	Kovacic 2017 [65, 66]	Shi 2021 [69]	Kutlu 2020 [67]	Paccione 2022 [68]	Zhang 2021 [71]	Ünal 2022 [70]
Number of spontaneous bowel movements per week	**IBS subgroup** **I [n=27] vs. C [n=23]:** Week 3: No difference between groups	**Week 4** **I [n=21] vs C [n=19]:** Mean 2.8 (SD 2.2) vs. 0.9 (SD 2.2); **p=0.001** Change in mean movements compared with baseline: I: 2.8 (SD 2.2) vs. 0.5 (SD 0.6); **p<0.001** C: 0.9 (SD 0.9) vs. 0.5 (SD 0.7)	NR	NR	NR	NR
Stool consistency	NR	**Week 4** **I [n=21] vs C [n=19]:** Patients with abnormally hard stools: 14% vs. 84%; p<0.001	NR	NR	NR	NR
Pain pressure threshold	NR	NR	NR	NR	NR	**Day 5** **I [n=27] vs C [n=26]:** Mean change in kg/cm^2: 3.2 vs. 1.6; **p<0.001**
Safety						
Procedure-related adverse events (n)	**I [n=57] vs. C [n=47]:** Week 3: Ear discomfort: 3 vs. 3 Adhesive allergy: 1 vs. 2 Syncope due to needle phobia: 0 vs. 1	NR	NR	**I [n=28] vs C [n=29]:** Week 2: 0 in both groups	NR	NR
Procedure-related serious adverese events (n)	**I [n=57] vs. C [n=47]:** Week 3: 0 in both groups	NR	NR	**I [n=28] vs C [n=29]:** Week 2: Chest discomfort and additional pain: 1 vs. 0	NR	NR
Comments	3 of the 10 patients withdrew due to side effects	None	None	One patient withdrew due to side effects	None	NR

[a] *≥30% in the weekly average of daily scores for worst abdominal pain and an increase of ≥1 spontaneous bowel movement per week from baseline*

[b] *Measured with a fibromyalgia diagnostic criteria form that computes an overall fibromyalgia severity (0-31 point scale, where higher numbers indicated more severe pain status) composed of a WPI score and a SSS score.*

[c] *Data for the two other treatment arms (active and sham meditative-based diaphragmatic breathing) were not extracted as they do not constitute standard care for fibromyalgia.*

Abbreviations:
BAS: Beck Anxiety Scale; BDS: Beck Depression Scale; CI: confidence interval; FDI: Functional Disability Inventory; FIQ: Fibromyalgia Impact Questionnaire; FU: follow-up; IBS: irritable bowel syndrome; IBS-QOL: irritable bowel syndrome quality of life; IBS-SSS: irritable bowel syndrome severity scoring system; IQR: interquartile range; MSQ: Migraine Specific Quality-of-Life Questionnaire; NRS: numeric rating scale; PFSD: Pain-Frequency-Severity-Duration; SAS: Self-Rating Anxiety Scale; SD: standard devation; SDS: Self-Rating Depression Scale; SF-36: 36-item Short Form Survey; SRS: Symptom Response Scale; SSRIs – selective serotonin reuptake inhibitors; SSS: symptom severity scale; STAI-C: State-Trait Anxiety Inventory for Children; VAS: visual analogue scale; WPI: widespread pain index

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [99].

Table A-3: Risk of bias – randomised controlled trials on acute postoperative pain, see [58]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Blank 2021 [64]	Pain	Some concern	Low	Low	Some concern	Low	**Some concern**
	Analgesia consumption	Some concern	Low	Low	Some concern	Low	
	Use of rescue medication	Some concern	Low	Low	Some concern	Low	
	Device-related adverse events	Some concern	Low	Low	Some concern	Low	
Lim 2022 [54]	Pain	Some concern	Low	Low	Some concern	Low	**Some concern**
	Analgesia consumption	Some concern	Low	Low	Some concern	Low	
	Device-related adverse events	Some concern	Low	Low	Some concern	Low	
Michalek-Sauberer 2007 [55]	Pain	High	Low	Low	Some concern	Low	**High**
	Analgesia consumption	High	Low	Low	Some concern	Low	
	Use of rescue medication	High	Low	Low	Some concern	Low	
	Device-related adverse events	High	Low	Low	Some concern	Low	
Zhou 2021 [56]	Pain	Some concern	Low	Low	Low	Low	**Low**
	Analgesia consumption	Some concern	Low	Low	Low	Low	
	Use of rescue medication	Some concern	Low	Low	Low	Low	
	Device-related adverse events	Some concern	Low	Low	Low	Low	

Table A-4: Risk of bias – randomised controlled trials on chronic pain, see [58]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Kovacic 2017 [65, 66]	Pain	Low	Low	Low	Low	Low	**Low**
	Physical functioning	Low	Low	Low	Low	Low	
	Symptom severity	Low	Low	Low	Low	Low	
	Device -related adverse events	Low	Low	Low	Low	Low	
Shi 2021 [69]	Pain	Some concern	Some concern	Low	Some concern	Low	**High**
	Symptom severity	Some concern	Some concern	Low	Some concern	Low	
Zhang 2021 [71]	Pain	Some concern	Low	Low	Low	Low	**Some concern**
	Symptom severity	Some concern	Low	Low	Low	Low	
Kutlu 2020 [67]	Pain	Some concern	Some concern	Low	Some concern	Low	**High**
	Symptom severity	Some concern	Some concern	Low	Some concern	Low	
Paccione 2022 [68]	Pain	Low	Low	Low	Low	Low	**Low**
	Symptom severity	Low	Low	Low	Low	Low	
	Device-related adverse events	Low	Low	Low	Low	Low	
Ünal 2022 [70]	Pain	Some concern	Some concern	Low	Some concern	Low	**High**
	Physical functioning	Some concern	Some concern	Low	Some concern	Low	
	Symptom severity	Some concern	Some concern	Low	Some concern	Low	

Table A-5: Evidence profile: efficacy and safety of aVNS versus sham treatment in patients with acute postoperative pain

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference or relative effect	Comparative effect/ Comments	
Pain (after 12 hours of treatment)									
1 [56] (n=78)	RCT	Not serious	NA	Not serious	Not serious	Publication bias suspected[a]	**NRS scores were significantly lower in the intervention group (data not reported)**	**Favours intervention (p<0.05)** **No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.**	⊕⊕⊕⊕ High (critical)
Pain (after 2-5 days of treatment)									
2 [54,55] (n=131)	RCT	Very serious[b]	Serious[c]	Not serious	Not serious	Publication bias suspected[a] Consistent effect across studies despite varied outcome measures.[e]	**Pain measured using different scales over different time periods**	**No apparent difference between groups in either of the studies.** **Statistical analysis of comparison not reported in one study.**	⊕⊕◯◯ Low (critical)
Analgesia consumption (number of times pressed analgesia pump over 12 hours of treatment)									
1 [56] (n=78)	RCT	Not serious	Not serious	Not serious	Not serious	Publication bias suspected[a]	**Intervention:2** **Sham: 3**	**Favours intervention (p=0.02)** **No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.**	⊕⊕⊕⊕ High (critical)
Analgesia consumption (over 2-5 days of treatment)									
2 [54,55] (n=127)	RCT	Very serious[b]	Serious[d]	Not serious	Not serious	Publication bias suspected[a] Consistent effect across studies despite varied outcome measures.[e]	**Measured using different units over different time periods**	**No apparent difference between groups in either of the studies.** **Statistical analysis of comparison not reported in one study.**	⊕⊕◯◯ Low (critical)
Use of rescue medication (over 12 hours of treatment)									
1 [56] (n=78)	RCT	Not serious	Not serious	Not serious	Not serious	Publication bias suspected[a]	**Risk with sham** **51 per 100**	**Risk with aVNS** **26 per 100**	**Favours intervention (RR 0.50, 95% CI 0.27, 0.93; p=0.004)** **No difference between groups for the 12-24 and 24-48 hour time periods after treatment cessation.**	⊕⊕⊕⊕ High (critical)
Use of rescue medication (over 2-5 days of treatment)									
2 [54,55] (n=135)	RCT	Very serious[b]	Serious[d]	Not serious	Not serious	Publication bias suspected[a]	**Risk with sham** **19 to 80 per 100**	**Risk with aVNS** **19 to 60 per 100**	**No difference between groups in either study.**	⊕⊕◯◯ Low (critical)

Certainty assessment							Summary of findings			Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference or relative effect		Comparative effect/ Comments	
Device related adverse events (2-5 days' follow-up)										
2 [54-56] (n=208)	RCT	Very serious[b]	Serious[f]	Not serious	Not serious	Publication bias suspected[a] Very low numbers of events in some studies[e]	**Risk with sham**	**Risk with aVNS**	**No difference between groups RR 1.81 (0.79, 4.15)**	⊕○○○ Very low (critical)
							8 per 100	**15 per 100**	**Adverse events included pruritus, ear discomfort and tiredness. Unclear if patients experienced more than one event.**	

Comments:

[a] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

[b] *Serious concerns regarding randomisation process and allocation concealment in all trials. Imbalance in baseline characteristics between groups in one study [55].*

[c] *Measured using different scales over different time periods.*

[d] *Measured using different units over different time periods.*

[e] *Upgraded certainty rating due to consistency of effect across studies despite varied outcome measures.*

[f] *Some inconsistency in numbers of adverse events across trials suggests that they may not have been documented systematically, particularly given their relatively minor nature.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕○ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕○○ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕○○○ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *aVNS – auricular vagus nerve stimulation; CI – confidence interval; NRS: numeric rating scale; RCT – randomised controlled trial; RR – risk ratio*

Sources: *Lim et al. 2022 [54], Michalek-Sauberer et al. 2007 [55], Zhou et al. 2022 [56]*

Table A-6: Evidence profile: efficacy and safety of aVNS versus non-electrical auricular acupuncture in patients with acute postoperative pain

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference [SD] or relative effect	Comparative effect/ Comments	
Pain (after 2-5 days of treatment)									
2 [55, 64] (n=151)	RCT	Very serious[a]	Serious[b]	Not serious	Not serious	Publication bias suspected[c] Consistent effect across studies despite varied outcome measures.	Pain measured using different scales	No difference between groups in either study	⊕⊕◯◯ Low (critical)
Analgesia consumption (over 2-5 days of treatment)									
2 [55, 64] (n=143)	RCT	Very serious[a]	Serious[b]	Not serious	Not serious	Publication bias suspected[c] Consistent effect across studies despite varied outcome measures.	Measured using different units over different time periods	No difference between groups in either study	⊕⊕◯◯ Low (critical)
Use of rescue medication (over 2 days of treatment)									
1 [55] (n=97)	RCT	Very serious[a]	Not serious	Not serious	Not serious	Publication bias suspected[c]	**Risk with acupuncture** 18 per 100	**Risk with aVNS** 19 per 100	**No difference between groups RR 1.08 (95% CI 0.44, 2.62)** ⊕⊕◯◯ Low (critical)
Device related adverse events (after 2-5 days of treatment)									
2 [55, 64] (n=151)	RCT	Very serious[a]	Serious[d]	Not serious	Not serious	Publication bias suspected[c]	**Risk with acupuncture** 18 per 100	**Risk with aVNS** 19 per 100	**No difference between groups RR 1.08 (95% CI 0.44, 2.62)** ⊕⊕◯◯ Low (critical)

***Comments**:*

[a] *Some concerns about allocation concealment and imbalance in baseline characteristics between the treatment groups in both trials.*

[b] *Different pain measures used across the studies.*

[c] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

[d] *Some inconsistency in numbers of adverse events across trials suggests that they may not have been documented systematically, particularly given their relatively minor nature.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕◯ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕◯◯ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕◯◯◯ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

***Abbreviations:** aVNS – auricular vagus nerve stimulation; CI – confidence interval; RCT – randomised controlled trial; RR – risk ratio; SD – standard deviation*

***Sources:** Blank et al. 2021 [64], Michalek-Sauberer et al. 2007 [55]*

Table A-7: Evidence profile: efficacy and safety of aVNS versus standard care in patients with acute postoperative pain

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference [SD] or relative effect	Comparative effect/ Comments	
Pain (numeric rating scale) after 72 hours of treatment									
1 [54] (n=40)	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	Intervention: 4.6 [2.3] Standard care: 4.2 [2.3]	No apparent difference between groups. Statistical analysis of comparison not reported in the study.	⊕⊕◯◯ Low (critical)
Analgesia consumption (MME over 5 days of treatment)									
1 [54] (n=40)	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	Intervention: 51.1 [56.6] Standard care: 42.8 [44.0]	No apparent difference between groups. Statistical analysis of comparison not reported in the study.	⊕⊕◯◯ Low (critical)
Use of rescue medication (opioids) over 5 days of treatment									
1 [54] (n=40)	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	**Risk with standard care** 70 per 100	**Risk with aVNS** 60 per 100	**No difference between groups RR 0.86 (95% CI 0.57, 3.14)**	⊕⊕◯◯ Low (critical)
Device related adverse events after 5 days of treatment									
1 [54] (n=40)	RCT	Serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	**Risk with standard care** 0	**Risk with aVNS** 5 per 100	**No difference between groups RR 0.86 (95% CI 0.54, 1.36)**	⊕⊕◯◯ Low (critical)

Comments:

[a] *Some concerns about allocation concealment and assessor blinding (open label study due to nature of comparator).*

[b] *Small sample size limits precision.*

[c] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕◯ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕◯◯ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕◯◯◯ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *aVNS – auricular vagus nerve stimulation; CI – confidence interval; MME – milligram morphine equivalent; NA – not applicable; RCT – randomised controlled trial; RR – risk ratio; SD – standard deviation*

Sources: *Lim et al. 2022 [54]*

Table A-8: Evidence profile: efficacy and safety of aVNS versus sham treatment in patients with chronic pain-related gastrointestinal disorders

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference [SD] or relative effect	Comparative effect/ Comments	
Pain in adults (≥18 years) (visual analogue scale after 4 weeks of treatment)									
1 [69] (n=40)	RCT	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	**Mean change** **Intervention: -3.1 [2.2]** **Sham: -1.1 [1.1]**	**Favours intervention (p=0.001)**	⊕○○○ Very low (critical)
Pain in youth (11-18 years) (PFSD median 9.2 weeks after end of 3-week treatment session)									
1 [65, 66] (n=104)	RCT	Not serious	Not serious	Not serious	Not serious	Publication bias suspected[c]	**Median change:** **Intervention: -8.4 (IQR -15.9, 0.0)** **Sham: 0 (IQR -9.0, 9.1)**	**Favours intervention (p=0.02)** **Result after 3 weeks of treatment also favours intervention (p<0.0001).**	⊕⊕⊕⊕ High (critical)
Physical functioning in youth (11-18 years) (PFSD median 9.2 weeks after treatment cessation)									
1 [65, 66] (n=104)	RCT	Not serious	Not serious	Not serious	Not serious	Publication bias suspected[c]	**Mean change** **Intervention: ↓36%** **Sham: 0%**	**Appears to favour intervention.** **Statistical analysis of comparison not reported in the study.**	⊕⊕⊕⊕ High (critical)
Symptom severity in adults (≥18 years) (IBS-SSS score after 4 weeks of treatment)									
1 [69] (n=40)	RCT	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	**Mean after treatment** **Intervention: 197.1 [39.6]** **Sham: 289.5 [94.4]**	**Favours intervention (p=0.001)** **Lower score is better**	⊕○○○ Very low (critical)
Symptom severity in youth (11-18 years) (SRS after 3 weeks of treatment)									
1 [65, 66] (n=104)	RCT	Not serious	Not serious	Not serious	Not serious	Publication bias suspected[c]	**Median after treatment** **Intervention: 3 (IQR 1.0, 4.8)** **Sham: 1 (IQR 0.0, 2.3)**	**Favours intervention (p=0.0003)** **Higher score is better** **No difference between groups median 9.2 weeks after treatment cessation (data not reported)**	⊕⊕⊕⊕ High (critical)

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference [SD] or relative effect	Comparative effect/ Comments	
Device related adverse events in youth (11-18 years) after 3 weeks of treatment									
1 [65, 66] (n=104)	RCT	Not serious	Not serious	Not serious	Serious[d]	Publication bias suspected[c]	**Risk with sham**	**Risk with aVNS**	⊕⊕⊕○ Moderate (critical)
							11 per 100	**7 per 100**	**No difference between groups RR 0.66 (95% CI 0.19, 2.32)** **Adverse events included ear discomfort and adhesive allergy. One event of syncope due to needle phobia in sham group was not included in the RR calculation.**

Comments:

[a] *Some concerns about allocation concealment, bias due to deviations from intended interventions and bias in outcome measures due to outcome assessors being aware of treatment allocation.*

[b] *Single blind study design and small sample size raises concerns regarding precision.*

[c] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

[d] *Small RCT and low number of events.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕○ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕○○ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕○○○ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *aVNS – auricular vagus nerve stimulation; CI – confidence interval; FDI – Functional Disability Inventory; IBS-SSS – irritable bowel syndrome severity scoring system; IQR – interquartile range; PFSD – Pain-Frequency-Severity-Duration; RCT – randomised controlled trial; RR – risk ratio; SD – standard deviation; SRS – Symptom Response Scale*

Sources: *Kovacic et al. 2017 [65], Krasaelap et al. 2020 [66], Shi et al. 2021 [69]*

Table A-9: Evidence profile: efficacy and safety of aVNS versus sham treatment in patients with chronic fibromyalgia at last follow-up (after two weeks of treatment)

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference or relative effect	Comparative effect/ Comments	
Pain (numeric rating scale)									
1 [68] (n=57)	RCT	Not serious	Not serious	Not serious	Serious[a]	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: -0.82** **Sham: -0.86**	**No apparent difference between groups.** **Statistical analysis of comparisons not reported in the study.**	⊕⊕⊕◯ Moderate (critical)
Pain (widespread pain index)									
1 [68] (n=57)	RCT	Not serious	Not serious	Not serious	Serious[a]	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: -1.50** **Sham: -1.69**	**No apparent difference between groups.** **Statistical analysis of comparisons not reported in the study.**	⊕⊕⊕◯ Moderate (critical)
Symptom severity (symptom severity scale)									
1 [68] (n=57)	RCT	Not serious	Not serious	Not serious	Serious[a]	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: --1.32** **Sham: -1.21**	**No apparent difference between groups.** **Statistical analysis of comparisons not reported in the study.**	⊕⊕⊕◯ Moderate (critical)
Device related adverse events									
1 [68] (n=57)	RCT	Not serious	Not serious	Not serious	Serious[a]	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Risk with sham** **0**	**Risk with aVNS** **4 per 100**	**No difference between groups RR 3.10 (95% CI 0.13, 73.12)** **The single adverse event involved chest discomfort and additional pain, leading to patient withdrawal.**	⊕⊕⊕◯ Moderate (critical)

Comments:

[a] *mall sample size limits precision.*

[b] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕◯ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕◯◯ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕◯◯◯ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *aVNS – auricular vagus nerve stimulation; CI – confidence interval; RCT – randomised controlled trial; RR – risk ratio.*

Sources: *Paccione et al. 2022 [68]*

Table A-10: Evidence profile: efficacy and safety of aVNS plus exercise versus exercise in women with chronic fibromyalgia at last follow-up (after four weeks of treatment)

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference Mean [SD]	Comparative effect/ Comments	
Pain (visual analogue scale)									
1 [67] (n=52)	RCT	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean after treatment** **Intervention: 2.6 [1.91]** **Exercise: 3.5 [1.73]**	**No difference between groups (p=0.08)** **Study only included women**	⊕○○○ Very low (critical)
Symptom severity (Fibromyalgia Impact Questionnaire score)									
1 [67] (n=52)	RCT	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean after treatment** **Intervention: 37.3 [19.48]** **Exercise: 41.9 [18.15]**	**No difference between groups (p=0.4)** **Lower score is better** **Study only included women**	⊕○○○ Very low (critical)

Comments:

[a] *Open label study due to nature of interventions. Some concerns about allocation concealment and deviations from intended interventions. Imbalance in baseline health-related quality of life measures between groups.*

[b] *Combination of open label study, baseline imbalances and small sample size raises concerns regarding precision.*

[c] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕○ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕○○ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕○○○ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *RCT – randomised controlled trial; SD – standard deviation*

Sources: *Kutlu et al. 2020 [67]*

Table A-11: Evidence profile: efficacy and safety of aVNS versus sham treatment in patients with chronic episodic migraine without aura at last follow-up (after four weeks of treatment)

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other considerations	Absolute difference	Comparative effect/ Comments	
Pain (visual analogue scale)									
1 [71] (n=59)	RCT	Serious[a]	Not serious	Not serious	Not serious	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: -17.4** **Sham: -4.1**	**Favours intervention (p=0.008)**	⊕⊕⊕◯ Moderate (critical)
Symptom severity (migraine days)									
1 [71] (n=59)	RCT	Serious[a]	Not serious	Not serious	Not serious	Publication bias suspected[b] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: -2.5** **Sham: -0.7**	**Favours intervention (p=0.02)**	⊕⊕⊕◯ Moderate (critical)
Symptom severity (migraine duration)									
1 [71] (n=59)	RCT	Serious[a]	Not serious	Not serious	Not serious	Publication bias suspected[b]	**Mean change** **Intervention: -1.5** **Sham: 0.4**	**Favours intervention (p=0.02)** **Time unit not specified in study**	⊕⊕⊕◯ Moderate (critical)

Comments:

[a] *Some concerns about allocation concealment.*

[b] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕◯ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕◯◯ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕◯◯◯ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *RCT – randomised controlled trial*

Sources: *Zhang et al. 2022 [71]*

Table A-12: Evidence profile: efficacy and safety of aVNS plus usual care versus usual care in patients with chronic myofascial pain syndrome at last follow-up (after five days of treatment)

Certainty assessment							Summary of findings		Certainty (Importance)
No. of studies (patients)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute difference Mean [SD]	Comparative effect/ Comments	
Pain (visual analogue scale)									
1 [70] (n=53)	RCT	Very serious[a]	Not serious	Not serious	Serious[c]	Publication bias suspected[d] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: -2.77** **Usual care: -1.96**	**Favours intervention (p<0.001)**	⊕○○○ Very low (critical)
Physical functioning (grip strength, kg)									
1 [70] (n=53)	RCT	Very serious[a]	Not serious	Serious[b]	Serious[c]	Publication bias suspected[d] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change** **Intervention: 2.1** **Usual care: 0.5**	**Favours intervention (p=0.001)**	⊕○○○ Very low (critical)
Symptom severity (Compass-31 score)									
1 [70] (n=53)	RCT	Very serious[a]	Not serious	Not serious	Serious[c]	Publication bias suspected[d] Unclear whether adjunctive treatments were used and standardised across treatment groups	**Mean change secretomotor subscale** **Intervention: -0.88 [1.295]** **Usual care: -0.12 [0.816]**	**Favours intervention (p=0.01) for secretomotor subscale only.** **Comparisons for the other five subscales were not statistically significant.**	⊕○○○ Very low (critical)

Comments:

[a] *Open label study due to nature of interventions. Slight imbalance in baseline symptom severity and health-related quality of life measures between groups.*

[b] *Physical grip strength measures only one aspect of physical function.*

[c] *Combination of open label study, baseline imbalances and small sample size raises concerns regarding precision.*

[d] *Difficult to determine but suspected. This is a new area of research, and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

GRADE Working Group grades of evidence [59]
⊕⊕⊕⊕ *High quality: We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕○ *Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕○○ *Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕○○○ *Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Abbreviations: *RCT – randomised controlled trial; SD – standard deviation*

Sources: *Unal et al. 2022 [70]*

Applicability table

Table A-13: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Population One: Acute postoperative pain The participants in the studies varied according to the type of surgeries being conducted, which included major bowel resection, elective Cesarian delivery, molar extraction and anterior cruciate ligament reconstruction. There was nothing in the patient selection procedures or demographics that suggested any of the populations were atypical of the types of people likely to undergo these operative procedures. Therefore, the patients included in the studies are likely to be representative of those who would undergo such surgeries in the Austrian health system. However, the results pertaining to these patient groups are not necessarily applicable to individuals undergoing other types of surgery. Population Two: Chronic pain The studies on abdominal pain-related gastrointestinal disorders encompassed both children, adolescents (aged 110 to 18 years) and adults (up to the age of 75 years), which covers the range of patients who would likely have these conditions in Austria. One of the two studies on fibromyalgia only included a very narrow population of adult pre-menopausal women (aged 18 to 50 years). While this reduced the likelihood of patients having confounding morbidities, it also means that this patient group is not necessarily representative of the types of patients who typically have fibromyalgia. The other study suffers from the same issue in that it included only patients aged 18 to 65 years who did not have any existing psychiatric disorders. Depression is a common comorbidity in patients with fibromyalgia (lifetime prevalence of 90% for depressive symptoms and 62% to 86% for major depressive disorder [100]) and fibromyalgia, which is usually diagnosed in middle age, becomes more common with age. Consequently, the patients included in these studies may not be representative of those with fibromyalgia in Austria. The populations included in the studies on episodic migraine (patients aged 18 to 45 years) and myofsacial pain syndrome (patients aged 20 to 60 years) were similarly limited. Consequently, the results may not be applicable to older patients with these conditions.
Intervention	The aVNS devices used in the studies are commonly available, although only one study used a device that has the CE mark. However, since generic transcutaneous electrical nerve stimulation devices with custom made electrodes can also be used to deliver aVNS, this is not necessarily a limiting factor in terms of applicability. Population Two: Chronic pain aVNS was used in conjunction with an exercise program in two studies (one on fibromyalgia and one on myofsascial pain). Exercise therapy is a mainstay of treatment for these conditions and would likely be used in conjunction with aVNS in clinical practice in Austria.
Comparators	Population One: Acute postoperative pain The comparators were some form of sham treatment, auricular acupuncture or standard care. Sham treatment and standard care are acceptable comparators that do not contravene usual clinical practice. However, auricular acupuncture is not a treatment that would be routinely used in the care of patients with acute postoperative pain in Austria. Population Two: Chronic pain The comparators were some form of sham treatment or standard care in the form of exercise therapy. Sham treatment is an acceptable comparator that does not contravene usual clinical practice and exercise therapy is a mainstay of treatment for patients with chronic pain.

Domain	Description of applicability of evidence
Outcomes	Population One: Acute postoperative pain The critical outcomes of pain, analgesia consumption and use of rescue medication were reported in most of the studies over the treatment period, which was up to 5 days following surgery. Considering that the main purpose of aVNS is to alleviate pain in the immediate postoperative period, these outcomes and length of follow-up are appropriate. The occurrence of device-related adverse events was reported in all studies. Population Two: Chronic pain The critical outcomes of pain and symptom severity were reported in most of the studies, whereas physical functioning was only reported in half of the included studies and adverse events were reported in only a third. Some measure of health-related quality of life was reported in four of the six studies. Most outcome measures were measured during or at the end of treatment, the duration of which ranged form five days to four weeks. The wide range of treatment lengths reflects the fact that the optimal treatment durations for various conditions have yet to be elucidated.
Setting	Population One: Acute postoperative pain The studies were conducted in the USA, Austria and China. The aVNS devices were deployed in the inpatient setting, which is appropriate for the patient groups being studied, by a surgeon, nurse or other clinician trained in the use of the device. This is reflective of the likely use of aVNS in the Austrian inpatient setting. Population Two: Chronic pain Two studies each were conducted in China and Turkey and one each in Norway and the USA.. Depending on the condition being treated, the aVNS devices were deployed by a physician, physiatrist or other relevant specialist in outpatient settings, such as a rehabilitation or gastroenterology clinic. This is reflective of the likely utilisation of the device in Austria.

Abbreviations: aVNS - auricular vagus nerve stimulation

List of ongoing randomised controlled trials

Table A-14: List of ongoing randomised controlled trials of aVNS

Identifier/ Trial name	Condition	Target enrollment	Intervention	Comparator	Primary outcome	Primary completion date/Status	Sponsor
Acute or postopterative pain							
NCT05439707	Patients undergoing arthroplasty	600	aVNS (device not stated)	Sham aVNS	Postoperative cognitive function Postoperative delirium Acute postoperative pain (VAS) Chronic postsurgical pain (Short Form McGill Pain Questionnaire and Neuropathic Pain Scale)	July 2024 Not yet recruiting	Xuzhou Central Hospital The Affiliated Hospital of Xuzhou Medical University The First People's Hospital of Xuzhou
Chronic pain							
NCT05543239 (RELAX)	Radiotherapy-related neuropathic pain	116	aVNS (tVNS 501, Jiangsu, China)	Sham aVNS	Change in pain intensity (NRS)	November 2023 Recruiting	Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University
ChiCTR2100042987	Complex regional pain syndrome post stroke	60	aVNS (device not stated) + comprehensive rehabilitation training	Comprehensive rehabilitation training	Performance-based impairment Inflammatory factors Functional magnetic resonance imaging of brain Change in pain intensity (NRS)	Not stated Recruiting	Zhejiang Provincial People's Hospital
NCT03434652	Cyclic vomiting syndrome	47	aVNS (Neuro-Stim System-2 BRIDGE, Innovative Health Solutions, LLC, Indiana, USA)	Sham aVNS	Nausea severity (Baxter Retching Faces Scale)	March 2021 Completed recruiting	Medical College of Wisconsin
NCT04177511	Chronic pelvic pain due to endometriosis	72	aVNS (TENS Eco Plus (Schwa Medico GmbH, Germany)	Standard treatment	Change of symptoms related to the pelvic pain	February 2025 Recruiting	Hopital Foch

Identifier/ Trial name	Condition	Target enrollment	Intervention	Comparator	Primary outcome	Primary completion date/Status	Sponsor
NCT05555485	Chronic pain related to opioid withdrawal (≥6 months)	60	aVNS (Sparrow®, Spark Biomedical, Inc., Texas, USA)	Sham aVNS	Opioid withdrawal symptoms (Clinical Opioid Withdrawal Scale)	October 2027 Not yet recruiting	The University of Texas Medical Branch, Galveston National Institute of Neurological Disorders and Stroke
NCT05646173	Chronic low back pain (≥3 months)	60	aVNS (Vagustim® device, Vagustim, California, USA) + home exercises	Ultrasound + TENS + home exercises	Oswestry Disability Index	February 2023 Recruiting	Istanbul Medipol University Hospital
NCT05527366	Non-specific neck pain	36	aVNS (Vagustim® device, Vagustim, California, USA)	Ultrasound + TENS + hot pack	Pain severity (VAS) Muscle strength Joint range of motion Disability (Neck Disability Index) Sleep quality (Pittsburgh sleep quality index)	March 2022 Completed	Okan University
NCT05500716	Temporoman-dibular joint dysfunction	50	aVNS (Vagustim® device, Vagustim, California, USA) + traditional rehabilitation program	Traditional rehabilitation program	Heart rate variability	June 2023 Recruiting	Bahçeşehir University
NCT04520516	Erosive hand osteoarthritis	148	aVNS (Vagustim® device, Vagustim, California, USA)	Sham aVNS	Change in self-reported hand pain (VAS)	April 2023 Active, not recruiting	Assistance Publique - Hôpitaux de Paris Schwa Medico GmbH (device lending)
NCT05387135	Knee osteoarthritis	68	aVNS (TENS 7000, Roscoe Medical, Ohio, USA)	Sham aVNS	Pain (VAS)	July 2021 Completed	Suez Canal University
NCT04381624	Knee osteoarthritis	70	aVNS (device not stated) + exercise program	Sham aVNS + exercise program	Pain (VAS)	December 2023 Not yet recruiting	Universidad de La Frontera

Abbreviations: aVNS = auricular vagus nerve stimulation; NRS = Numeric Rating Scale; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale

Literature search strategies

Search strategy for Cochrane

Search date: 07.12.2022	
ID	Search
#1	MeSH descriptor: [Pain] explode all trees
#2	(pain*) (Word variations have been searched)
#3	(post-op*) (Word variations have been searched)
#4	(postop*) (Word variations have been searched)
#5	(post-surg*) (Word variations have been searched)
#6	(postsurg*) (Word variations have been searched)
#7	MeSH descriptor: [Migraine Disorders] explode all trees
#8	(migraine*) (Word variations have been searched)
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	MeSH descriptor: [Vagus Nerve Stimulation] explode all trees
#11	((“vagus nerve*“ OR vagus OR “tenth cranial nerve*“ OR “10th cranial nerve*“ OR “cranial nerve* x“ OR “pneumogastric nerve*“ OR “pneumo-gastric nerve*“ OR “nerve* xs“ OR “nervi vagi“ OR “vagal nerve*“ OR “vagal receptor*“ OR “vagosympathetic trunk*“ OR “vago-sympathetic trunk*“ OR “vagus trunk*“ OR vagal OR auric*) NEAR (“transcutaneous electrical nerve stimulation*“ OR tens OR tan OR electroacupuncture* OR “electro-acupuncture*“ OR electrotherap* OR “electro-therap*“ OR stimul* OR neurostim* OR “neuro-stim*“ OR neuromodul* OR “neuro-modul*“ OR electrostimul* OR “electro-stimul*“ OR acupuncture* OR electroacupuncture* OR “electro-acupuncture*“)):ti,ab,kw
#12	(aVNS):ti,ab,kw
#13	(a-VNS):ti,ab,kw
#14	(taVNS):ti,ab,kw
#15	(ta-VNS):ti,ab,kw
#16	(tVNS):ti,ab,kw
#17	(t-VNS):ti,ab,kw
#18	(tcVNS):ti,ab,kw
#19	(nVNS):ti,ab,kw
#20	(„percutaneous electric nerve field stimulation*“) (Word variations have been searched)
#21	(PENFS):ti,ab,kw
#22	(IB-Stim*) (Word variations have been searched)
#23	(NeuroStim) (Word variations have been searched)
#24	(Neuro-Stim) (Word variations have been searched)
#25	(NEMOS*) (Word variations have been searched)
#26	(„Primary Relief*“) (Word variations have been searched)
#27	(P-Stim*) (Word variations have been searched)
#28	(Soterix*) (Word variations have been searched)
#29	(SDZ-II) (Word variations have been searched)
#30	(SNM-FDC01) (Word variations have been searched)
#31	(„TENS 7000“) (Word variations have been searched)
#32	(TENS7000) (Word variations have been searched)
#33	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#9 AND #33
#35	(conference proceeding):pt
#36	(abstract):so (Word variations have been searched)
#37	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#38	#35 OR #36 OR #37
#39	#34 NOT #38
Total hits: 407	

Search strategy for Embase

Search date: 07.12.2022	
ID	Search
#1	‚pain'/exp
#2	pain*
#3	‚post-op*'
#4	postop*
#5	‚post-surg*'
#6	‚migraine'/exp
#7	migraine*
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	‚vagus nerve stimulation'/exp
10	(‚vagus nerve*' OR vagus OR ‚tenth cranial nerve*' OR ‚10th cranial nerve*' OR ‚cranial nerve* x' OR ‚pneumogastric nerve*' OR ‚pneumo-gastric nerve*' OR ‚nerve* xs' OR ‚nervi vagi' OR ‚vagal nerve*' OR ‚vagal receptor*' OR ‚vagosympathetic trunk*' OR ‚vago-sympathetic trunk*' OR ‚vagus trunk*' OR vagal OR auric*) NEAR/3 (‚transcutaneous electrical nerve stimulation*' OR tens OR tan OR ‚electroacupuncture*' OR ‚electrotherap*' OR stimul* OR neurostim* OR ‚neuro stim*' OR neuromodul* OR ‚neuro modul*' OR electrostimul* OR ‚electro stimul*' OR acupuncture* OR electroacupuncture* OR ‚electro acupuncture*')
#11	avns:ti,ab
#12	‚a-vns':ti,ab
#13	‚transcutaneous vagus nerve stimulator'/exp
#14	‚tavns':ti,ab
#15	‚ta-vns':ti,ab
#16	tvns:ti,ab
#17	tcvns:ti,ab
#18	nvns:ti,ab
#19	‚percutaneous electric nerve field stimulation*'
#20	penfs:ti,ab
#21	‚ib-stim'
#22	neurostim
#23	‚neuro-stim'
#24	‚nemos'/exp
#25	nemos
#26	‚primary relief'
#27	‚p stim'
#28	soterix
#29	‚sdz-ii'
#30	‚snm-fdc01'
#31	‚tens 7000'
#32	tens7000
#33	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR 19,610 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#8 AND #33
#35	#8 AND #33 AND [randomized controlled trial]/lim
#36	((double NEXT/1 blind*):de,ab,ti) OR placebo*:ab,ti OR blind*:ab,ti
#37	#34 AND #36
#38	#34 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)
#39	(‚meta analysis (topic)'/exp OR ‚meta analysis'/exp OR ((meta NEXT/1 analy*):ab,ti) OR metaanaly*:ab,ti OR ‚systematic review (topic)'/exp OR ‚systematic review'/exp OR ((systematic NEXT/1 review*):ab,ti) OR ((systematic NEXT/1 overview*):ab,ti) OR cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR ‚science citation index':ab,ti OR bids:ab,ti OR ((reference NEXT/1 list*):ab,ti) OR bibliograph*:ab,ti OR ‚hand search*':ab,ti OR ((manual NEXT/1 search*):ab,ti) OR ‚relevant journals':ab,ti OR ((‚data extraction':ab,ti OR ‚selection criteria':ab,ti) AND review/it)) NOT (letter/it OR editorial/it OR (‚animal'/exp NOT (‚animal'/exp AND ‚human'/exp)))
#40	#34 AND #39
#41	#35 OR #37 OR #38 OR #40
#42	(#35 OR #37 OR #38 OR #40) AND ([english]/lim OR [german]/lim)
#43	#42 AND ‚Conference Abstract'/it
#44	#42 NOT #43
Total hits: 631	

Search strategy for Medline via Ovid

Search date: 07.12.2022	
ID	Search
#1	exp Pain/
#2	pain*.mp.
#3	post-op*.mp.
#4	postop*.mp.
#5	post-surg*.mp.
#6	postsurg*.mp.
#7	exp Migraine Disorders/
#8	migraine*.mp.
#9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Vagus Nerve Stimulation/
#11	(exp Vagus Nerve/ or (nervus vagus or vagus nerve* or tenth cranial nerve* or cranial nerve* x or pneumogastric nerve* or nerve* xs or vagal or auric*).mp.) adj4 (exp Transcutaneous Electric Nerve Stimulation/ or TENS.ti,ab. or tAN.ti,ab. or exp Electroacupuncture/ or exp Electric Stimulation Therapy/ or (stimul* or neurostim* or neuro-stim* or neuromodul* or neuro-modul* or electrostimul* or electro-stimul* or acupuncture* or electroacupuncture* or electro-acupuncture*).mp.)
#12	aVNS.ti,ab.
#13	a-VNS.ti,ab.
#14	taVNS.ti,ab.
#15	ta-VNS.ti,ab.
#16	tVNS.ti,ab.
#17	t-VNS.ti,ab.
#18	tcVNS.ti,ab.
#19	nVNS.ti,ab.
#20	percutaneous electric nerve field stimulation*.mp.
#21	PENFS.ti,ab.
#22	IB-Stim*.mp.
#23	NeuroStim.mp.
#24	Neuro-Stim.mp.
#25	NEMOS*.mp.
#26	Primary Relief*.mp.
#27	P-Stim*.mp.
#28	Soterix*.mp.
#29	SDZ-II.mp.
#30	SNM-FDC01.mp.
#31	TENS 7000.mp.
#32	TENS7000.mp.
#33	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
#34	9 and 33
#35	limit 34 to randomized controlled trial
#36	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
#37	34 and 36
#38	limit 34 to (meta analysis or „systematic review“)
#39	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or „research synthesis“ or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not „psycinfo database“) or pubmed or scopus or „sociological abstracts“ or „web of science“).ab. or („cochrane database of systematic reviews“ or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.

#40	34 and 39
#41	35 or 37 or 38 or 40
#42	limit 41 to (english or german)
#43	remove duplicates from 42
Total hits: 462	

Search strategy for HTA Database (INATHTA)

Search date: 07.12.2022	
ID	Search
#1	„Vagus Nerve Stimulation“[mhe]
#2	aVNS
#3	a-VNS
#4	taVNS
#5	ta-VNS
#6	tVNS
#7	t-VNS
#8	tcVNS
#9	nVNS
10	auric*
#11	percutaneous electric nerve field stimulation*
#12	PENFS
#13	IB-Stim*
#14	NeuroStim
#15	Neuro-Stim
#16	NEMOS*
#17	„Primary Relief“
#18	P-Stim
#19	Soterix
#20	SDZ-II
#21	SNM-FDC01
#22	„TENS 7000“
#23	TENS7000
#24	(TENS7000) OR („TENS 7000“) OR (SNM-FDC01) OR (SDZ-II) OR (Soterix) OR (P-Stim) OR („Primary Relief“) OR (NEMOS*) OR (Neuro-Stim) OR (NeuroStim) OR (IB-Stim*) OR (PENFS) OR (percutaneous electric nerve field stimulation*) OR (auric*) OR (nVNS) OR (tcVNS) OR (t-VNS) OR (tVNS) OR (ta-VNS) OR (taVNS) OR (a-VNS) OR (aVNS) OR („Vagus Nerve Stimulation“[mhe])
#25	((TENS7000) OR („TENS 7000“) OR (SNM-FDC01) OR (SDZ-II) OR (Soterix) OR (P-Stim) OR („Primary Relief“) OR (NEMOS*) OR (Neuro-Stim) OR (NeuroStim) OR (IB-Stim*)
Total hits: 27	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH