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Efficacy of transcutaneous vagus nerve stimulation as treatment for patients with depression

Guerriero G, Bernhardsson S, Gunnarsson S, Ioannou M, Liljedahl SI, Magnusson K, Steingrimsson S, Svanberg T, Wartenberg C

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Efficacy of transcutaneous vagus nerve stimulation as treatment for patients with depression

[Effekter av transkutan vagusnervstimulering som behandling vid depression]

Guerriero G[1,2]*, Bernhardsson S[3], Gunnarsson S[1], Ioannou M[1,2], Liljedahl SI[1,2], Magnusson K[4], Steingrimsson S[1,2], Svanberg T[4], Wartenberg C[3]

[1]Region Västra Götaland, Psykiatri Affektiva, Department of Psychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]University of Gothenburg, Sahlgrenska Academy, Institute of Neuroscience and Physiology, Gothenburg, Sweden
[3]Region Västra Götaland, HTA-centrum, Gothenburg, Sweden
[4]Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden

*Corresponding author

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Regional activity based HTA 2020:119

Table of contents

1. Abstract

Background: Depression is a common mental illness associated with significant disability and suffering. Current treatment strategies include psychopharmacological therapy, psychotherapy, and in certain cases electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS). However, further treatment options are needed. Vagus nerve stimulation (VNS) by surgical implantation of an electrode placed on one of the branches of the vagus nerve in the neck was approved for treatment resistant depression by the European Medicines Agency (EMA) in 2001 and by the US Food and Drug Administration (FDA) in 2005. To overcome the risks of invasive VNS, non-invasive, transcutaneous vagus nerve stimulation (tVNS) methods have recently been developed, aiming to stimulate vagal afferents, either at the external ear (auricular vagus nerve branch) or the neck (cervical part of the vagus nerve).

Objectives: The objective of this Health Technology Assessment (HTA) was to assess whether tVNS is an efficacious treatment for patients with depression compared with sham tVNS, treatment as usual, or no treatment. Mortality, self-harm, depressive symptoms, and health-related quality of life (HRQoL) were considered critical outcomes for decision making. Important outcomes were level of anxiety symptoms, medication use, everyday functioning, complications, and patients' experiences of treatment.

Methods: A systematic literature search was conducted in June 2020 in PubMed, Embase, the Cochrane Library, PsycInfo, CINAHL, and a number of HTA-databases. The included articles were critically appraised. Certainty of evidence was assessed using the GRADE approach.

Main results: Three studies using different devices for transcutaneous stimulation at the auricular branch of the vagus nerve, with different stimulation characteristics, frequency and duration of tVNS in patients with mild to moderate depression were included in this HTA. One RCT (n=37) and one cohort study (n=160) compared tVNS with sham tVNS. Both studies had major study limitations, some problems with directness, and serious imprecision. One case series (n=12) collected data on complications. None of the studies included measures to verify that stimulation of the vagus nerve was achieved during treatment. No studies comparing tVNS with treatment as usual or no treatment were identified.

None of the included studies reported data regarding the outcomes *mortality, self-harm, HRQoL*, *level of functioning, medication use,* and *patients' experience of treatment*. *Depressive symptoms* were evaluated based on clinician assessment and self-assessment in the RCT and the cohort study. While the RCT reported statistically significantly larger improvement in self-assessed depression symptoms after two weeks of tVNS treatment compared with sham tVNS, there was no corresponding significant difference in the clinician-assessed scores. The cohort study reported statistically larger improvement in both clinician- and self-assessed depressive symptoms after tVNS compared with sham tVNS. *Anxiety symptoms* were only reported in the cohort study. Both clinician- and self-assessments showed a larger reduction of symptoms in the tVNS group than in the sham group. As *complications,* mild to moderate transient events including tinnitus, diurnal sleepiness, tension headaches, nausea, paresthesia at the electrodes site during the stimulation were reported.

Concluding remarks: Studies of tVNS used different devices, frequency and duration to treat patients with mild to moderate depression. Based on one RCT and one cohort study, both with major study limitations, and some indirectness and imprecision, it is uncertain whether tVNS compared with sham tVNS, reduces depression and anxiety symptoms in patients with mild to moderate depression (very low certainty of evidence, GRADE ⊕◯◯◯). Mortality, self-harm, HRQoL, medication use, level of functioning and patients' experience of treatment have not been investigated. Complications noted during tVNS treatment were mild to moderate transient events of tinnitus, diurnal sleepiness, tension headaches, nausea and paresthesia at the stimulation site. No studies comparing tVNS with treatment as usual or no treatment were identified. Further research is needed to understand if there are benefits and risks of tVNS treatment in patients with depression.

2. Svensk sammanfattning – Swedish summary

Bakgrund: Depression är ett vanligt psykiskt tillstånd kopplat till kraftigt nedsatt funktion och lidande. Nuvarande behandlingsalternativ inkluderar läkemedel, psykoterapi och i vissa fall elektrokonvulsiv terapi eller repetitiv transkraniell magnetisk stimulering (rTMS). Behovet av fler effektiva behandlingsmetoder är stort. Vagusnervstimulering (VNS) introducerades i Europa 2001 och i USA 2005, i form av kirurgisk implantation av en elektrod på en gren av vagusnerven på halsen. Då denna metod medför patientrisker har nyligen ett icke-invasivt alternativ utvecklats i form av transkutan vagusnervstimulering (tVNS) på halsen eller på ytterörat.

Syfte: Syftet med denna HTA-rapport var att utvärdera om tVNS är en effektiv behandlingsmetod för patienter med depression jämfört med simulerad tVNS, standardbehandling eller ingen behandling. Kritiska utfallsvariabler i analysen var dödlighet, självskadebeteende, symtom på depression, och hälsorelaterad livskvalitet. Viktiga utfallsvariabler var ångestsymtom, läkemedelsförbrukning, funktionsförmåga, komplikationer, och patientens upplevelse av behandlingen.

Metod: En systematisk litteratursökning genomfördes i juni 2020 i PubMed, Embase, Cochrane Library, PsycINFO, Cinahl och ett antal HTA-databaser. Studiernas kvalitet utvärderades och GRADE-systemet användes för att bedöma tillförlitligheten hos de sammanvägda resultaten.

Resultat: Tre studier, där olika apparatur och stimulering hade använts i behandlingen av patienter med lindrig till medelsvår depression, inkluderades i rapporten. En randomiserad kontrollerad studie (RCT) på 37 patienter och en kohortstudie på 160 patienter jämförde tVNS med simulerad tVNS. Båda studier hade allvarliga brister i design eller genomförande samt problem gällande överförbarhet. Det begränsade materialet innebär allvarliga problem avseende precisionen. En fallserie på 12 patienter inkluderades för information om biverkningsprofilen. Ingen av studierna inkluderade mätningar för att bekräfta att vagusnerven stimulerades under tVNS behandlingen. Ingen studie jämförde tVNS med standardbehandlingar eller ingen behandling.

Symtom på depression utvärderades med hjälp av klinisk bedömning och självrapportering i RCTn och kohortstudien. I RCTn rapporterades efter två veckors tVNS behandling en större förbättring av självrapporterade depressionssymtom men inte i den kliniska bedömningen, jämfört med simulerad tVNS. I kohortstudien sågs signifikant större förbättring i både självrapporterade och kliniskt bedömda depressionssymtom efter tVNS jämfört med simulerad tVNS. *Ångestsymtom* rapporterades endast i kohortstudien med en signifikant minskning av både kliniskt bedömda och självrapporterade symtom bland efter tVNS jämfört med simulerad tVNS. Ingen av studierna undersökte effekter på *dödlighet, självskadebeteende, hälsorelaterad livskvalitet, funktionsförmåga, läkemedelsförbrukning* eller *patienters upplevelse av behandlingen*.Som *komplikationer* rapporterades lindriga till måttliga övergående biverkningar i form av tinnitus, sömnighet, huvudvärk, illamående, samt parestesi på de ställen där elektroderna satt under behandlingen.

Sammanfattande kommentarer: De få studier som har gjorts på tVNS har använt olika utrustning och behandlingsprotokoll. Baserat på en RCT och en kohortstudie, båda med allvarliga brister i studiekvalitet samt vissa brister i överförbarhet och precision, är det osäkert huruvida tVNS minskar depressions- och ångestsymtom mer än simulerad tVNS hos patienter med mild till måttlig depression (låg tillförlitlighet, GRADE ⊕◯◯◯). Dödlighet, självskadebeteende, hälsorelaterad livskvalitet, läkemedelsförbrukning, funktion och patienterfarenheter har inte studerats i de inkluderade studierna. Vid tVNS noterades lindriga till måttliga övergående biverkningar i form av tinnitus, sömnighet, huvudvärk, illamående, samt domningar på de ställen där elektroderna satt under behandlingen. Inga studier jämförde tVNS med standardbehandling eller ingen behandling och mer forskning behövs för att förstå risker och nytta av tVNS-behandling vid depression.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 25th of November, 2020

Regional board for quality assurance of activity-based HTA	
Bergenheim, Anna	PT, PhD
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Bernhardsson, Susanne	PT, Associate professor
Hakeberg, Magnus	OD, Professor
Jivegård, Lennart	MD, Senior university lecturer
Larsson, Anders	MD, PhD
Nelzén, Olle	MD, Associate professor
Petzold, Max	Statistician, Professor
Rylander, Christian	MD, Associate professor
Sjögren, Petteri	DDS, PhD
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Svanberg, Therese	HTA librarian
Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

No studies comparing tVNS with treatment as usual or no treatment were identified. Findings regarding the comparison of tVNS and sham tVNS are summarised below.

Outcomes	Study design Number of studies	Relative effect	Absolute effect tVNS – sham tVNS	Certainty of evidence GRADE
Outcomes critical for decision making				
Mortality, self-harm, HRQoL - no data available in included studies				NA
Depressive symptoms	1 RCT 1 cohort study	-	**RCT:** Between-group difference in change from baseline to 2 weeks (mean) BDI Δ = -8.2, *p=0.004* HDRS-17 Δ = 1.2, *ns* **Cohort study:** Between-group difference in change from baseline to 4 weeks (mean (95% CI)) HDRS-24: Δ=*-6.1 (-4.5 to -8.3)*, *p<0.0001* SDS: Δ=*-9.1 (-5.5 to -12.4), p<0.0001*	⨁◯◯◯[1]
Outcomes important for decision making				
Anxiety symptoms	1 cohort study	-	Between-group difference in change from baseline to 4 weeks (mean (95% CI)) HAM-A: Δ=*-3.0 (-1.6 to -5.6), p<0.0001* SAS: Δ=*-5.1 (0.5 to -7.2), p=0.01*	⨁◯◯◯[2]
Everyday functioning, medication use, patients' experience of treatment - no data available in included studies				NA
Complications	1 RCT 1 cohort study 1 case series		Mild to moderate transient events, including tinnitus, diurnal sleepiness, tension headaches, nausea, paresthesia at the electrodes site during the stimulation	NA

HRQoL: Health-related quality of life; BDI: Beck's Depression Inventory (range 0–63); HDRS-17 and HDRS-24: Hamilton Depression Rating Scale HDRS-17 (range 0–52) and HDRS-24 (range 0–96); NA: not assessed; ns: not statistically significant; SDS: Self-rating Depression Scale (range 20–80); HAM-A: Hamilton Anxiety Rating Scale (range 0–56); SAS: Self-rating Anxiety Scale (range 20–80); tVNS: transcutaneous vagus nerve stimulation

[1]Downgraded for serious study limitations, serious indirectness, serious imprecision and some inconsistency.
[2]Based on one cohort study, downgraded for serious study limitations and serious imprecision.

Certainty of evidence

High certainty ⨁⨁⨁⨁	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⨁⨁⨁◯	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 certainty ⨁⨁◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⨁◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

BDI	Becks Depression Inventory
CBT	Cognitive Behavioural Therapy
DBS	Deep brain stimulation
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAM-A	Hamilton Anxiety Rating Scale
HDRS-17	Hamilton Depression Rating Scale - 17
HDRS-24	Hamilton Depression Rating Scale - 24
HRQoL	health-related quality of life
iVNS	Invasive vagus nerve stimulation
MDD	major depressive disorder
MST	Magnetic seizure therapy
RCT	Randomised controlled trial
rTMS	Repetitive transcranial magnetic stimulation
SAS	Self-rating Anxiety Scale
SDS	Self-rating Depression Scale
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
taVNS	Transcutaneous auricular vagus nerve stimulation
tcVNS	Transcutaneous cervical vagus nerve stimulation
tVNS	Transcutaneous vagus nerve stimulation
tDCS	Transcranial direct current stimulation
TENS	Transcutaneous electrical nerve stimulation
tVNS	Transcutaneous vagus nerve stimulation
VN	Vagus nerve
VNS	Vagus nerve stimulation

5. Background

Disease/disorder of interest and its degree of severity

Depression is a common mental disorder associated with significant disability and suffering (Whiteford et al., 2013, World Health Organization [WHO], 2017). Moreover, depression is highly correlated with premature death mainly due to suicide and cardiovascular diseases (Machado et al., 2018).

Depression is considered a syndrome, i.e. a constellation of symptoms. It may manifest as a single episode, or in chronic affective disorders such as bipolar disorder and recurrent depressive disorder (Goodwin and Jamison, 2007). The most prominent symptoms of depression are persistently depressed mood and diminished interest in activities, leading to severe functional impairment in daily life. Other common symptoms are sleep and appetite disturbances, cognitive inhibition, and feelings of guilt (American Psychiatric Association [APA], 2013). Suicidal and psychotic behaviour may occur and hospitalization may hence be required (Lam et al., 2009).

The aetiology of depression is not fully understood, but likely both complex and heterogeneous. The disorder is thought to be the product of interactions between biological factors, personality traits, as well as social and environmental factors (Garcia-Toro and Aguirre, 2017). At a biological level, abnormalities linked to depression have been identified in cerebral structures of the limbic system, amygdala, hippocampus and thalamus (Pandya et al., 2012). Furthermore, theoretical pathogenetic pathways include desynchronization of neuronal activity, dysfunction in neuroplasticity and inflammation factors. The concept behind exploring transcutaneous vagus nerve stimulation (tVNS) as treatment in patients with depression is that the electrical stimulation of the vagal afferents, either at the external ear (auricular branch of the vagus nerve) or the neck (cervical part of the vagus nerve) may affect these pathways in depression (Conway and Xiong, 2018).

Prevalence and incidence

More than 264 million people suffer from depression worldwide (WHO, 2017). Approximately 800,000 commit suicide every year, making it the second leading cause of death in individuals aged 15-29 years (WHO, 2017).

In Sweden, the lifetime risk for depression has been estimated to be 36% for women and 23% for men (Mattisson et al., 2005). According to a survey by the Public Health Agency of Sweden, the one-year prevalence of clinician-diagnosed depression was about 4% in Sweden (Folkhälsomyndigheten, 2017).

Present treatment

Treatment of depression varies depending on symptom severity and grade of depression. Lifestyle changes are usually recommended as the first step in patients with mild symptoms and without psychiatric history. Psychotherapy should be offered in cases of mild to moderate forms of depression, while physical exercise or antidepressant medication can be prescribed as alternative treatment options (National Collaborating Centre for Mental Health, 2020). In moderate to severe depression, antidepressant medication or psychotherapy should be used. In more severe cases of depression, antidepressants are considered to be more effective than psychotherapy, although synergic effects may occur (Cuijpers et al., 2014, Socialstyrelsen, 2020a).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are considered the standard first-line antidepressant medication (Socialstyrelsen, 2020a). However, less than one-third of patients receiving standard antidepressants in clinical trials experience remission (Thase et al., 2005).
In recent treatment guidelines, the addition of atypical antipsychotic agents to ongoing serotonin reuptake inhibitor treatment is often put forward as alternative for patients who do not respond to SSRIs/SNRIs (Simons et al., 2017). Unfortunately, atypical antipsychotic agents show only small-to-moderate benefits in the treatment of depression and are associated with risks for troublesome side effects. They are hence far from optimal drugs for the treatment of SSRI/SNRI-resistant depression (Spielmans et al., 2013).

As a complement to other antidepressant treatment, several neurostimulation methods have been used (Müller et al., 2018). Electroconvulsive therapy (ECT) is the most effective and widely spread method in clinical practice. However, the use of ECT is limited by the risk of cognitive side effects (such as memory loss) and the requirement of anaesthesia (Getty and Faziola, 2017, Uppal et al.; 2010). Memory loss may complicate the treatment of individuals who have co-occurring trauma-related disorders, for whom the exposure to traumatic memories may be clinically indicated as part of treatment (Bisson et al., 2007).

In the last decade, repetitive transcranial magnetic stimulation (rTMS) has been offered as treatment alternative in some tertiary care centres. However, the place of rTMS in the antidepressant treatment algorithm has not been clearly defined (Lefaucheur et al., 2020). Furthermore, financial concerns for the healthcare provider and time burdens for the patients limit its broader use (Sonmez et al., 2019).

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

In Sweden, the majority of patients with depression (about 70%) are diagnosed and treated in primary care (Statens beredning för medicinsk och social utvärdering [SBU], 2004). Patients with therapy-resistant depression, at high risk of suicide or presenting with comorbid psychiatric conditions, are commonly referred to secondary care centres. A first evaluation normally takes place within three months after referral (Socialstyrelsen, 2019a). The patient usually undergoes a new assessment at the referred psychiatric unit. Patients may also initiate a self-referral to the secondary care system. In some cases, patients may need acute hospital admission due to the intensity of symptoms, severe functional impairment, treatment resistance, or suicide risk. Compulsory care is required in some cases, especially in depression with psychotic features. Hospital admission is usually mandated (non-elective) after presentation at the psychiatric emergency room, although direct or non-elective admission may also be necessary for some patients with ongoing outpatient psychiatric care for safety purposes.

Number of patients per year who undergo the current treatment regimen

Prescription rates of antidepressant medication, especially SSRIs, are relatively high in Sweden. Among adults in 2015, more than 12% of women and 6% of men were undergoing treatment with antidepressant medication (Socialstyrelsen, 2019b). According to online data from the National Patient Registry, admission rates of adult patients with depression were up to 120 inpatient admissions per 100,000 citizens in Sweden in 2019, with an average length of hospital stay of 15 days (Socialstyrelsen, 2020b).

Present recommendations from medical societies or health authorities

The Swedish national guidelines from the National Board of Health and Welfare state that treatment options depend on the type of depression and its severity (mild, moderate or severe) as also mentioned above (Socialstyrelsen, 2020a). In recurrent depressive disorder or severe depression, antidepressant medication, ECT, and lithium are strongly recommended (Socialstyrelsen, 2020a).

Vagus nerve stimulation, both by the method at issue in this report (that is, tVNS), and by invasive VNS, is considered experimental and is therefore not included in clinical treatment algorithms and guidelines in Sweden at present.

6. Health Technology at issue: Transcutaneous electrical vagus nerve stimulation

Neurostimulation, or neuromodulation, is an expanding area of research and clinical interest in the treatment of depression. Neurostimulation treatments use electrical or magnetic stimulation targeting specific brain regions with noninvasive techniques, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST), as well as invasive surgical techniques, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Most of these neurostimulation treatments have been studied and are used in patients with treatment-resistant depression who have failed to respond to standard treatments (Milev et al., 2016).

The vagus nerve (VN), one of the cranial nerves, largely consists of fibers that transmit nerve impulses from the periphery to the brain. Electrical stimulation of the VN provides stimulation to the nucleus tractus solitarii, which in turn is able to modulate multiple regions of the brain via its neuronal connections to anatomically distributed subcortical and cortical regions of the brain (Nemeroff et al., 2006). The invasive form of vagus nerve stimulation (iVNS) requires surgical implantation of a pulse generator underneath the skin of the chest. The pulse generator is connected to an electrode placed onto one of the branches of the VN in the neck. This invasive method was approved in 1997 for the treatment of refractory epilepsy, in 2001 as an adjunct long-term treatment for treatment-resistant depression by the European Medicines Agency (EMA) in Europe, and in 2005 by the Food and Drug Administration (FDA) in the United States of America. The approval was based on documentation focusing on the risk profile of iVNS and provided only limited data on the efficacy of this method in treatment-resistant depression. Surgical risks, technical challenges, and potential side effects have limited the use of iVNS in clinical practice.

To overcome the risks of iVNS, non-invasive transcutaneous vagus nerve stimulation (tVNS) methods have been developed. Currently, there are two main ways to apply tVNS. One is to superficially apply stimulation on the cervical part of the vagus nerve using a specially designed device, such as gammaCore™, (transcutanous cervical vagus nerve stimulation or tcVNS) and the other is to apply stimulation on the ear (transcutanous auricular vagus nerve stimulation or taVNS). The rationale of stimulation on the ear (taVNS) is based on anatomical studies demonstrating that certain parts of the ear area (concha and lower half of the back ear over the mastoid process) have afferent VN distribution. It is assumed that stimulation on the auricular branch of VN can activate the inferior ganglion, which projects to the nucleus tractus solitarii (He et al., 2013), and in this way could produce therapeutic effects that are similar to those of regular VNS (Hein et al., 2013, Rong et al., 2016, Stefan et al., 2012).

The exploration of tVNS is not limited to the treatment of depression and epilepsy, but is currently being investigated for a variety of disorders including headache, tinnitus, atrial fibrillation, schizophrenia, and chronic pain (Yap et al., 2020).

The described methods of tVNS use different devices, and stimulation protocols and there is currently no firm evidence regarding location and form of stimulation to achieve effect. The most commonly used devices are gammaCore for the stimulation at a neck site (FDA approved for acute and/or prophylactic treatment of primary headache), and NEMOS® (CE marked for the treatment of resistant epilepsy) for the stimulation of the auricular branch of VN on the ear. In addition to NEMOS and gammaCore, both manufactured specifically for tVNS, stimulation can also be performed by transcutaneous electrical nerve stimulator (TENS) devices, typically used in pain management, such as TENS-200, V-TENS PLUS or TENS-NET 2000. The first two devices are often selected for convenience as they provide an easy-to-use package that includes stimulation electrodes, while other devices, such as TENS-200, often require custom-made electrodes. Most of the devices are portable battery powered control units allowing patients to administer tVNS by themselves at home while doing something else (e.g., listening music) (Yap et al., 2020). The stimulation parameters used in studies on depressed patients vary from 15 minutes stimulation duration, once or twice per day with 1.5 Hz unipolar rectangular waves at 0-600 mA for two weeks (Hein et al., 2013) to 30 minutes stimulation duration twice a day, with 20 Hz continuous sinusoidal waves at 4-6 mA for 4 weeks (Rong et al., 2016).

There is an unmet need for additional treatment options for patients with depression. Given the non-invasive nature of the method, tVNS – if shown safe and effective – could potentially be a first line option for patients who refuse/do not tolerate pharmacological treatment, or a second/third line treatment (alone or as add-on strategy) for patients experiencing no response/remission to first line treatment.

7. Focused question

Is transcutaneous electrical vagus nerve stimulation, compared with sham-treatment, treatment as usual, or no treatment, an effective intervention for patients with depression with respect to the outcomes mortality, self-harm, depressive symptoms, health-related quality of life, anxiety/emotion dysregulation, everyday functioning, complications, medication use, or patients' experience of treatment?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Adults or adolescents with a clinician-diagnosed depression (including both uni- and bipolar depression and post-partum depression)
I	Transcutaneous electrical vagus nerve stimulation
C	1: Sham treatment 2: Treatment as usual, e.g. pharmacological, psychotherapy, other stimulation method (electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), invasive VNS) 3: No treatment
O	Critical for decision-making • Mortality (including completed suicide) or suicide attempts • Self-harm (with or without suicidal intention) • Depressive symptoms (including suicide ideation) using validated scales (including analysis of remission and relapse as well as long term effects) • Health-related quality of life Important for decision-making • Level of anxiety symptoms and/or emotion dysregulation measured with validated instruments • Everyday functioning (restored Activities of Daily Living, return to work) according to validated scales or administrative data • Complications (Note – worsening in depressive symptoms is evaluated as part of effect measures and not as part of complications) • Use of medication for depression treatment • Patients' own experience of treatment (based on qualitative studies)

8. Methods

Systematic literature search (Appendix 1)

This HTA was registered with PROSPERO (CRD42020196465). During June 2020 two authors (TS, KM) performed systematic searches in PubMed, Embase, the Cochrane Library, PsycInfo, CINAHL and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

Included studies and their design and patient characteristics are presented in Appendix 2. Excluded studies and reasons for exclusion are presented in Appendix 3. The included RCT and cohort study were critically appraised by all authors using checklists from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). The results of each study have been summarised per outcome in Appendix 4.

Data per outcome were extracted by one author and checked for accuracy by another. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). Certainty of evidence was assessed using the GRADE approach (Guyatt et al., 2008) for each outcome for which data were available in the included studies.

Patient involvement

The PICO was reviewed by a representative from the patient organisation BALANS – an organisation for patients with different psychiatric diagnoses, including depression and bipolar depression. The patient representative was informed about the HTA project and asked to provide input on the PICO. The patient representative confirmed that the outcomes at issue were relevant and emphasised the value of patients' autonomy during treatment. The patient organisation was also asked to review the draft Swedish summary and a representative confirmed that the summary was comprehensible from a patient perspective.

Ongoing research

A search in Clinicaltrials.gov (2020-08-18) using the search terms ((vagus nerve stimulation OR vagus nerve stimulations OR vagal nerve stimulation OR vagal nerve stimulations OR VNS) AND (transcutaneous OR non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable) OR (tNS OR taVNS)) AND (depression OR depressions OR depressive OR depressed OR antidepression OR antidepressive OR antidepressed OR anti-depression OR anti-depressive OR anti-depressed) identified 34 trials. Four of these were relevant for our PICO.

9. Results

Search results and study selection (Appendix 1)

The literature search identified 179 articles after removal of duplicates. After reading the abstracts 159 articles were excluded. Another six articles were excluded by two authors (TS, KM) after reading the articles in full text. The remaining 14 articles were sent to all participants of the project group, and three articles (1 RCT, 1 cohort study and 1 case series) were finally included in the HTA report (Appendix 2).

Included studies

Three studies were included in this HTA report, all of which included patients with mild to moderate depression. All studies applied the stimulation on the ear (auricular branch of the vagus nerve). One article (Hein et al., 2013) provided results of an RCT with a total of 37 patients, reporting the data both as overall results and divided into two small sub-studies that differed in the stimulation methods used. In this study patients were randomized to two weeks of treatment with tVNS or sham tVNS in addition to continued standard treatment with antidepressant medication and/or cognitive behavioral therapy. One cohort study (Rong et al., 2016) included 160 patients who received tVNS or sham tVNS for 4 weeks. In this study patients had to discontinue any psychiatric medication two weeks prior to study treatment. The third included study was a case series (Trevizol et al., 2016) collecting information on complications in 12 patients. In all three studies, a total of 109 patients received tVNS and 88 patients received sham treatment as control. No studies comparing tVNS with standard treatment or with no treatment were identified. Both the RCT and the cohort study were assessed as having major study limitations, some problems with indirectness, and the limited material implies serious imprecision. All included studies are described in Appendix 2. None of the three studies included any measure to verify that stimulation of the vagus nerve was achieved. However, analyses of fMRI measurements in a subset of patients in the study reported by Rong et al., (2016) showed some changes in cortical functional connectivity after tVNS stimulation compared with sham tVNS (Liu et al., 2016, Fang et al., 2017, and Tu et al., 2018).

Results per outcome

Outcomes critical for decision-making

None of the included studies reported data regarding the critical outcomes ***mortality, self-harm, or HRQoL.***

Depressive symptoms (Appendix 4.1)

Depressive symptoms were reported as outcome in the RCT and the cohort study. Table 1 provides information on the different measurement scales used in the studies to assess depressive symptoms.

Table 1:Measurement scales for assessment of depressive symptoms

Abbreviation	Scale	Range	Administration
BDI	Beck's Depression Inventory	0 – 63 (higher values imply increased depressive symptoms)	Self-rating
HDRS-17	Hamilton Depression Rating Scale (with 17 items)	0-52 (higher values imply increased depressive symptoms	Clinician-assessed
HDRS-24	Hamilton Depression Rating Scale (with 24 items)	0-96 (higher values imply increased depressive symptoms	Clinician-assessed
SDS	Self-rating Depression Scale	20 – 80 (higher values imply increased depressive symptoms)	Self-rating

The RCT comprised two sub-studies, each of which compared a different mode of tVNS (self-administered vs clinician administered, and different devices) with sham tVNS treatment. Depressive symptoms were measured at baseline and after two weeks of treatment, both by self-report scales (BDI) and by clinician assessment (HDRS-17). On the aggregated level, the change from baseline in the self-reported data showed a larger decrease in the BDI score after tVNS (from 27.9 to 15.3 point) compared with sham tVNS (from 30.0 to 25.6) with a statistically significant advantage for the tVNS treatment (p=0.004). However, clinician rated scales did not show a significant difference in change (decrease from 16.6 to 11.2 in tVNS vs from 18.1 to 11.5 in sham tVNS, ns). In the cohort study, changes in depression symptoms were assessed at baseline and after 4 weeks of treatment. Clinician assessment by HDRS-24 showed a significantly larger reduction in the tVNS group than in the sham group (between-group difference of -6.1, 95% CI -4.5 to -8.3, p<0.0001). And the same pattern was observed in the self-reported data (SDS scale) (between-group difference of -9.1, 95% CI -5.5 to -12.4, p<0.0001). Also, 24 patients in the tVNS group vs none in the sham group achieved response (according to the established definition of a 50% reduction in HDRS-24) and 3 patients in the tVNS group compared with none in the sham group achieved remission (according to the established definition of an HDRS-24 score <8).

Conclusion: It is uncertain whether tVNS reduces depressive symptoms compared with sham tVNS in patients with mild to moderate depression (very low certainty of evidence, GRADE ⊕◯◯◯).

Outcomes important for decision-making

None of the included studies reported data regarding the outcomes ***everyday functioning, medication use and patients´ experience of treatment.***

Anxiety symptoms (Appendix 4.2)

Anxiety symptoms were reported in the cohort study (Rong et al., 2016). Table 2 provides information on the different measurement scales used in the study to assess anxiety symptoms.

Table 2: Measurement scales for assessment of anxiety symptoms

Abbreviation	Scale	Range	Administration
HAM-A	Hamilton Anxiety Rating Scale	0 – 56 (higher values imply increased anxiety symptoms)	Clinician-assessed
SAS	Self-rating Anxiety Scale	20 – 80 (higher values imply increased anxiety symptoms)	Self-rating

In this study clinician assessment using HAM-A showed a statistically significantly larger reduction in the tVNS group than in the sham group (between-group difference of -3.0 (95% CI -1.6 to -5.6, p<0.0001) and likewise a larger reduction in the self-reported anxiety levels based on the Self-rating Anxiety Scale (SAS) (between-group difference of -5.1, 95% CI 0.5 to -7.2, p=0.01).

Conclusion: It is uncertain whether tVNS compared with sham tVNS reduces anxiety symptoms in patients with mild to moderate depression (very low certainty of evidence, GRADE ⊕◯◯◯).

Complications (Appendix 4.3)

Adverse effects were systematically collected by diary booklets in the cohort study (Rong et al., 2016); publications on the other two included studies (Hein et al., 2013, and Trevizol et al., 2016) do not describe how data on side effects were collected. In the RCT (Hein et al., 2013), it is stated that none of the patients reported any unpleasant sensations during or after the stimulation procedures, nor were any adverse side effects reported after the treatment.

Further, no effects on heart rate, blood pressure or blood test parameters were observed after a 2-week tVNS intervention period. In the cohort study (Rong et al., 2016) including 160 patients, the only adverse effect reported in both tVNS (2 cases) and sham tVNS group (3 cases) was mild tinnitus or aggravation of pre-existing tinnitus with full recovery after stopping the tVNS/sham tVNS without further treatment. In the case series of 12 patients (Trevizol et al., 2016) no severe adverse events were reported. Mild to moderate events included diurnal sleepiness after the stimulation, tension headaches with no need for medication, nausea, and paresthesia at the site of the electrodes during the stimulation. No side effects were reported at the one-month follow-up.

Conclusion: Complications reported by patients treated with tVNS were mild to moderate transient events of tinnitus, diurnal sleepiness, tension headaches, nausea and paresthesia at the stimulation site.

10. Ethical aspects

Research on the use of tVNS in patients with depression is in its infancy. The risk benefit profile of tVNS as treatment in this patient population is unclear, as reliable data on both benefits and side effects are lacking and there is no other experience in using this treatment method. Therefore, use of the method should be limited to research settings. In the included studies, the mode of administration as well as the duration and level of stimulation differ. Accordingly, the way to ensure an intended transcutaneous stimulation of the vagus nerve is not clearly defined.

There is a need for additional treatment options for patients with depression. For instance, Koenig et al. (2019) report that 40% of youth do not respond to first line interventions for depression. One valued aspect of care communicated to the authors of this report by their regionally representative patient reference group was an increased autonomy in treatments for depression. Currently available psychopharmacological treatment requires adherence to prescription, and slow dose adjustments. If future research provides evidence for the efficacy and safety of tVNS, this method might allow for increased autonomy for patients if they can choose timing and extent of treatment themselves.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

tVNS has never been used in the management of depression at Sahlgrenska University Hospital or in the Region Västra Götaland. There is a lack of consensus on the stimulation parameters and the limited knowledge about the method would require a tight monitoring by caregivers, with frequent control visits. According to the publications included in this HTA report, the support needed by the patients to undergo the treatment protocols was limited. The patients could either be assisted by the staff in inpatient settings or, after being trained, manage the administration of the stimulation by themselves in both in- and outpatient settings. Therefore, the introduction of the technology in the clinical practice is mostly limited by an insufficient knowledge about the method and data on its efficacy. This makes it almost impossible to make a time prediction for a potential implementation of the technology that, otherwise, may require only some weeks/months.

Consequences of the new health technology for personnel

Current treatment of patients with depression e.g. with antidepressants, psychotherapy or in severe cases ECT, often requires a high frequency of contacts with health care. This care is often comprised of prescribers, care givers, support staff, telephone operator, psychologists, due to renewal of prescriptions, monitoring of side effects, need of support, and the intensity of psychosocial interventions. As indicated above, it is too early to tell whether and how tVNS could be an additional treatment option in this context.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

It is difficult to make any prediction of the possible consequences related to implementation of the technique at this stage.

12. Economic aspects

Present costs of currently used technologies

Treatment of depression varies depending on the severity of the symptoms and the type of depression. A recent study including a cost analysis of patients with mild to moderate depression in Region Västra Götaland showed an annualised cost per patient of approximately 5,000 SEK (Holst et al., 2018). Additionally, studies have shown that the economic cost from production losses related to depression-caused sick-leave is several orders of magnitude higher than the direct healthcare costs (Olesen et al., 2012).

Expected costs of the new health technology

Assuming a cost (list price) of about 25,000 SEK for a tVNS device, discount rate 3%, 12 weeks of treatment time per patient and a technology life length of 5 years, the cost per patient for the device will be approximately 1,325 SEK. This cost only covers acquisition of the device. If used as an additional treatment, the cost would need to be added to the current costs per patient. Device costs may be lower, if it can be shown that commonly used TENS devices that are available at lower costs can be used for tVNS treatment.

Total change in costs

As described in Section 9, information about the benefit and risks with tVNS treatment in patients with depression is limited. Therefore, use of tVNS should be limited to research settings. The information below is to be considered as very early estimates of costs in clinical practice.
The new technology is expected to cost about 1,325 SEK per patient and treatment episode (assuming a period of 12 weeks). The total change in costs will depend on the number of patients treated. Considering the high incidence and prevalence of the disease (about 4% incidence/year, ie about 42,500 patients in VGR), the total cost could be substantial if offered in full scale to patients who do not tolerate pharmacological treatment as first line treatment (assumption 10%–20%) and as a second/third line treatment (alone or as add-on strategy) for patients experiencing no response/remission with first line treatment (assumption: 25%–60%).
Using the lower assumptions for the proportion of patients who could be candidates for a new treatment (first-line treatment for about 4,250 patients and second/third line treatment for about 9,500 patients), offering tVNS to all these patients could lead to a cost for acquisition of tVNS devices of about 18 million SEK per year in VGR.
As described in Section 9, it is uncertain whether tVNS has beneficial effect on depressive symptoms.

If tVNS would lead to substantial improvements in health-related quality of life and reduced symptoms of depression, it is possible that it would reduce future costs of healthcare utilisation as well as pharmaceutical use. In the absence of significant evidence for this we have not made any such calculations in this report and assume that the costs will be additional to present costs of current treatments for these patients.

Possibility to adopt and use the new technology within the present budget

Implementation of tVNS technology for patients with a clinician-diagnosed depression is not likely to be possible within the present budget, but would instead most likely require additional funding to the healthcare sector and/or imply that other healthcare services are displaced.

Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost analyses of tVNS in patients with a clinician-diagnosed depression were identified.

13. Discussion

Summary of main results

This analysis is based on one RCT and one cohort study comparing tVNS with sham tVNS, and one case series. For the outcome depression symptoms, inconsistent data were seen in the clinician-assessed vs the patient-reported scales in the RCT. The cohort study reported favourable results for tVNS compared with sham tVNS. For anxiety symptoms data are only available from the cohort study; even here, favourable results were reported for tVNS. However, due to major study limitations, some inconsistency, indirectness and serious imprecision, our confidence in the observations regarding both outcomes is very low (GRADE ⊕◯◯◯). Several outcomes included in the PICO were not assessed in any of the included studies. These were: mortality, self-harm, quality of life, everyday functioning, medication use and patient´s own experience of the treatment. Only one of the three included studies provided details on the collection of information regarding adverse events, whilst the other two publications report safety results without details on how these data were collected. Complications reported by patients treated with tVNS were mild to moderate transient events of tinnitus, diurnal sleepiness, tension headaches, nausea and paresthesia at the stimulation site. As additional information, it may be noted that the main complications of iVNS are infections, vocal cord paresis, lower facial weakness, bradycardia, and asystole (Ben-Menachem, 2001) – ie side effects that are considered to be related to the surgical procedure and the position of the implanted device rather than the vagus nerve stimulation.

None of the three studies included any measure to verify that stimulation of the vagus nerve was achieved. Analyses of fMRI measurements in a subset of patients in the study reported by Rong et al., (2016) showed some changes in the central nervous system regarding cortical functional connectivity after tVNS stimulation compared with sham tVNS (Liu et al., 2016, Fang et al., 2017, and Tu et al., 2018). Still, these findings cannot be regarded as direct evidence for VNS stimulation as they could, for example, be due to trigeminus or great auricular nerve stimulation.

Overall completeness and applicability of evidence

Although the PICO was defined broadly in order not to exclude publications in the field, only three articles could be included. The controlled studies have major study limitations, some indirectness, and the limited material implies serious imprecision.

Major problems are also the heterogeneity in treatment protocols (device, frequency, intensity and duration of tVNS treatment) and patient populations (heterogeneity of the population of patients with different types and severity of depression, outpatient vs. inpatients; drug free vs. ongoing standard treatment).

Agreements and disagreements with other studies and reviews

The findings of this HTA report are in agreement with two systematic reviews which both interpret the evidence as limited yet indicate positive effects of tVNS in patients with depression (Cimpianu et al., 2017, Wu et al., 2018). However, these two publications include studies (Liu et al., 2016, Tu et al., 2018) that we excluded from our report because of duplication/re-analysis of data derived from the original trial published by Rong et al.(2016).

Implications for research

As conclusions are limited by the paucity and quality of studies and the heterogeneity of treatment modalities and study population, further well-designed RCTs are required to address the scientific knowledge gaps described below. Moreover, up to now there is no information on long-term effects of tVNS in patients with depression, which could be of particular interest since a cohort study of iVNS has shown a delayed onset of the antidepressant effect (Aaronson et al., 2017).

Scientific knowledge gaps

A number of questions remain:

Method of tVNS stimulation

- Which anatomical site is suitable for tVNS?
- Which stimulation parameters are to be used if aiming to achieve antidepressant effect?

Efficacy of tVNS stimulation

- Is tVNS an effective treatment for patients with depression?

Patient population

- Can specific subpopulations benefit from tVNS?
- Is tVNS effective in treating treatment resistant depression?
- Is tVNS effective for treatment of other psychiatric conditions?

Administration

- Is self-administered tVNS comparable with clinician-administered tVNS in terms of efficacy?
- How does self-administration of tVNS impact the compliance to treatment and the quality of life of patients?
- Can tVNS be self-administered effectively while engaging in other activities?

Ongoing research

The search for ongoing trials related to our PICO in clinicaltrials.org initially identified 34 studies. Among these, we identified 4 studies that we consider relevant for the question at issue in this report:

- A multi-center RCT planning to include 470 patients with mild to moderate depression. The study is designed to examine whether transcutaneous electrical cranial-auricular acupoint stimulation (TECAS) is non-inferior to the antidepressant drug escitalopram in treating mild-to-moderate depression and to evaluate the depressive subtypes who are suitable for the TECAS treatment (study ongoing, expected to complete 2021, ClinicalTrials.gov identifier *NCT03909217*).

- An RCT planning to include 106 patients with mild to moderate depression. This study is designed to compare the therapeutic effects of Auricular Concha Electro-acupuncture with Citalopram in patients with major depressive disorder (MDD) (study was expected to complete 2019 ClinicalTrials.gov identifier *NCT03607331*);
- An RCT planning to include 90 patients with depression. The study is designed to investigate the efficacy of taVNS on major depressive disorder and rheumatoid arthritis in patients with this comorbidity (study expected to complete 2021. ClinicalTrials.gov identifier *NCT04037111*);
- An RCT planning to include 80 patients with recurrent depression. This RCT is designed to investigate sex-dependent impact of expiratory-gated tVNS on the modulation of the stress response circuity and associated physiology in major depressive disorder (study expected to complete 2024, ClinicalTrials.gov identifier *NCT04448327*);

14. Participants in the project

The question was nominated by

Giuseppe Guerriero, MD, MSc, Specialist in Psychiatry, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, Gothenburg, Sweden
Mathias Alvidius, line manager, Dept of Psychiatry for Affective Disorders, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating healthcare professionals

Giuseppe Guerriero, MD, MSc, Specialist in Psychiatry, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, Gothenburg, Sweden
Sara Gunnarsson, MD, Resident in Psychiatry, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, Gothenburg, Sweden
Michael Ioannou, MD, Specialist in Psychiatry, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, Gothenburg, Sweden
Sophie I. Liljedahl, PhD, Clinical Psychology, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, and Dept of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
Steinn Steingrimsson, MD, Specialist in Psychiatry, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychiatry for Affective Disorders, and Associate professor, Dept of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Participants from the HTA-centrum

Constanze Wartenberg, Psychologist, PhD, Region Västra Götaland, HTA-centrum, Gothenburg, Sweden
Susanne Bernhardsson, Physiotherapist, Associate professor, Region Västra Götaland, HTA-centrum, Gothenburg, Sweden
Therese Svanberg, Librarian, Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden
Kajsa Magnusson, Librarian, Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Borås, Sweden
Mikael Svensson, Health economist, Region Västra Götaland, HTA-centrum and Professor, University of Gothenburg, The Sahlgrenska Academy, Health Metrics, Gothenburg, Sweden
Pernilla Rönnholm, project coordinator, Region Västra Götaland, HTA-centrum, Gothenburg, Sweden

External reviewers

Ulla Karilampi, Psychologist, PhD, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Psychotic Disorders, Gothenburg, Sweden
Anders Larsson, MD, PhD, Region Västra Götaland, Södra Älvsborgs Sjukhus, Dept of Neurology, Borås, Sweden

Declaration of interests

None of the participants have any conflicts of interest to declare.

Project time

The HTA was accomplished during the period of 4 June 2020 – 25 November 2020.
Literature searches were made on 22 June 2020.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Is transcutaneous electrical vagus nerve stimulation, compared with sham-treatment, treatment as usual, or no treatment, an effective intervention for patients with depression with respect to the outcomes mortality, self-harm, depressive symptoms, health-related quality of life, anxiety/emotion dysregulation, everyday functioning, complications, medication use, or patients' experience of treatment?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

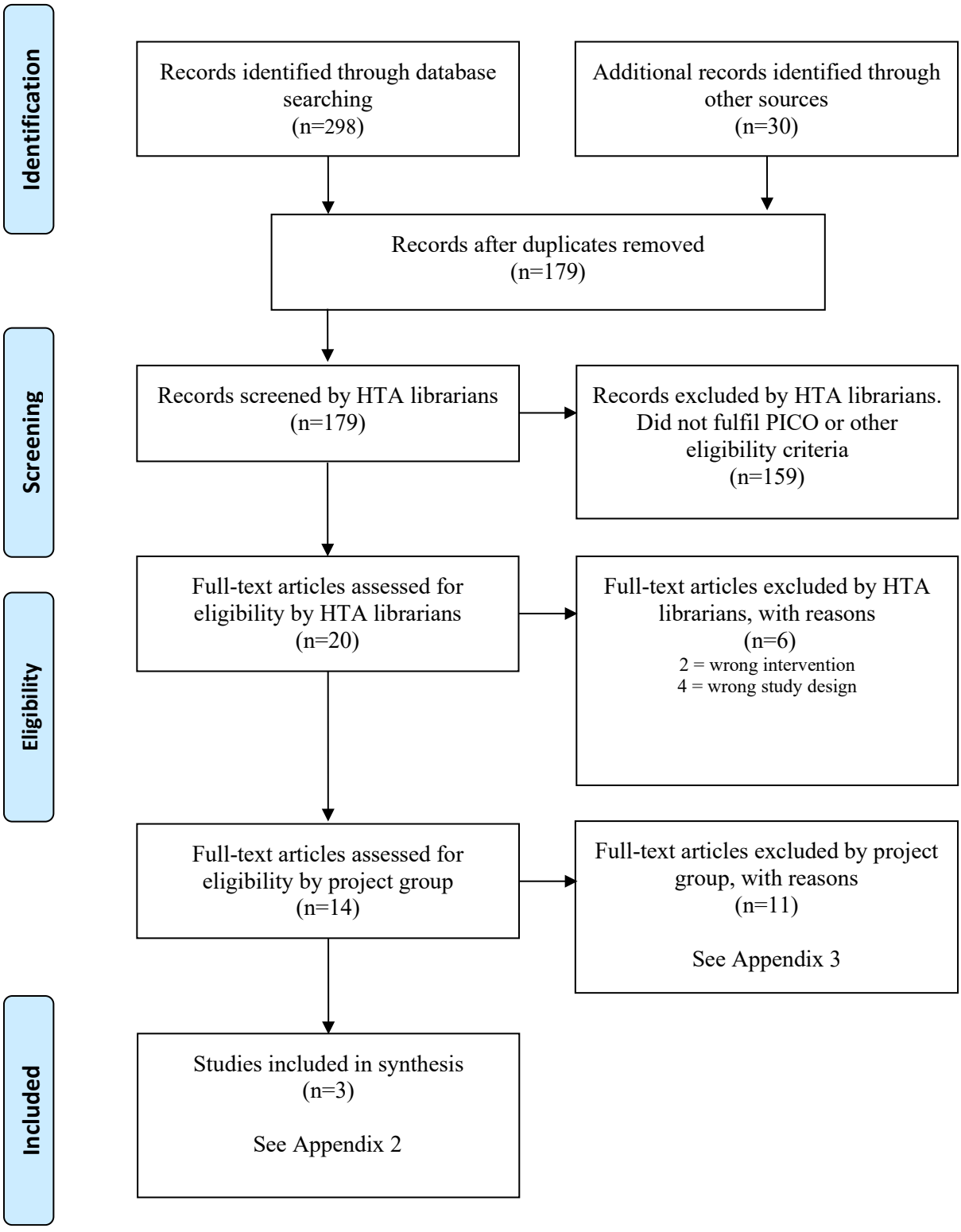
P	Adults or adolescents with a clinician-diagnosed depression (including both uni- and bipolar depression and post-partum depression)
I	Transcutaneous electrical vagus nerve stimulation
C	1: Sham treatment 2: Treatment as usual, e.g. pharmacological, psychotherapy, other stimulation method (electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), invasive VNS) 3: No treatment
O	Critical for decision-making • Mortality (including completed suicide) or suicide attempts • Self-harm (with or without suicidal intention) • Depressive symptoms (including suicide ideation) using validated scales (including analysis of remission and relapse as well as long term effects) • Health-related quality of life Important for decision-making • Level of anxiety symptoms and/or emotion dysregulation measured with validated instruments • Everyday functioning (restored Activities of Daily Living, return to work) according to validated scales or administrative data • Complications (Note – worsening in depressive symptoms is evaluated as part of effect measures and not as part of complications) • Use of medication for depression treatment • Patients' own experience of treatment (based on qualitative studies)

<u>Eligibility criteria</u>
Study design:
Randomised controlled trials
Non-randomised controlled studies
Case series ($n \geq 10$ patients) for rate of complications and qualitative studies for patients´ own experience

Language:
English, Swedish, Norwegian, Danish, Italian

Publication date:
2000-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 22 June 2020
No. of results: 87

Search	Query	Items found
#35	**Search #20 AND #23 Filters: Publication date from 2000/01/01; Swedish; Norwegian; Italian; English; Danish**	**87**
#25	Search #20 AND #23 Filters: Publication date from 2000/01/01	93
#24	Search #20 AND #23	96
#23	Search #21 OR #22	507059
#22	Search depression*[tiab] OR depressive*[tiab] OR depressed[tiab] OR antidepress*[tiab] OR anti-depress*[tiab]	470057
#21	Search Depression[Mesh] OR Depressive Disorder[Mesh]	214864
#20	Search #16 OR #18 OR #19	686
#19	Search tVNS[tiab] OR taVNS[tiab]	140
#18	Search "Transcutaneous Electric Nerve Stimulation"[Mesh] AND (vagus nerve OR vagal nerve)	240
#16	Search #14 AND #15	574
#15	Search transcutaneous[tiab] OR non-invasive[tiab] OR noninvasive[tiab] OR auricular[tiab] OR non-implantable[tiab] OR nonimplantable[tiab]	198706
#14	Search #12 OR #13	11435
#13	Search vagus nerve stimulation OR vagus nerve stimulations OR vagal nerve stimulation OR vagal nerve stimulations OR VNS[tiab]	11435
#12	Search "Vagus Nerve Stimulation"[Mesh]	1536

Database: Embase 1974 to 2020 June 19 (OvidSP)
Date: 22 June 2020
No. of results: 114

#	Searches	Results
1	vagus nerve stimulation/	10402
2	((vagus adj5 nerve adj5 stimulation$1) or (vagal adj5 nerve adj5 stimulation$1)).af.	12055
3	VNS.ab,kw,ti.	3509
4	1 or 2 or 3	12915
5	(transcutaneous or non-invasive or noninvasive or auricular or non-implantable or nonimplantable).ab,kw,ti.	287022
6	4 and 5	1077
7	transcutaneous electrical nerve stimulation/	1854
8	((vagus adj5 nerve) or (vagal adj5 nerve)).ab,kw,ti.	15541
9	7 and 8	76
10	(tVNS or taVNS).ab,kw,ti.	213
11	6 or 9 or 10	1115
12	exp postnatal depression/	3100
13	exp involutional depression/	272

14	exp major depression/	63848
15	exp endogenous depression/	895
16	exp depression/	470036
17	exp bipolar depression/	6224
18	exp perinatal depression/	4044
19	exp long term depression/	5460
20	exp treatment resistant depression/	3157
21	(depression* or depressive* or depressed or antidepress* or anti-depress*).ab,kw,ti.	637211
22	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	784834
23	11 and 22	177
24	limit 23 to (embase or medline)	124
25	limit 24 to yr="2000 -Current"	121
26	**limit 25 to (danish or english or italian or norwegian or swedish)**	**114**

Database: The Cochrane Library
Date: 22 June 2020
No. of results:
Clinical trials: 27

ID	Search	Hits
#1	MeSH descriptor: [Vagus Nerve Stimulation] explode all trees	77
#2	(vagus nerve stimulation OR vagus nerve stimulations OR vagal nerve stimulation OR vagal nerve stimulations):ti,ab,kw (Word variations have been searched)	864
#3	(VNS):ti,ab,kw (Word variations have been searched)	486
#4	#1 OR #2 OR #3	970
#5	(transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable):ti,ab,kw (Word variations have been searched)	22520
#6	#4 AND #5	377
#7	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees	1847
#8	(vagus nerve OR vagal nerve):ti,ab,kw (Word variations have been searched)	1298
#9	#7 AND #8	40
#10	(tVNS OR taVNS):ti,ab,kw (Word variations have been searched)	133
#11	#6 OR #9 OR #10	386
#12	MeSH descriptor: [Depression] explode all trees	11836
#13	MeSH descriptor: [Depressive Disorder] explode all trees	11938
#14	(depression* OR depressive* OR depressed OR antidepress* OR anti-depress*):ti,ab,kw (Word variations have been searched)	86304
#15	#12 OR #13 OR #14	86353
#16	#11 AND #15 with Cochrane Library publication date Between Jan 2000 and Dec 2020	49
#17	(clinicaltrials or trialsearch):so with Publication Year from 2000 to 2020, with Cochrane Library publication date Between Jan 2000 and Dec 2020, in Trials	325867
#18	**#16 NOT #17**	**27**

Database: PsycInfo (EBSCOhost)
Date: 22 June 2020
No. of results: 43

#	Undran	Resultat
S12	**S7 AND S10** **Utökning - Sök med likvärdiga ämnesord; Sök med relaterade ord** **Begränsa genom att Language: - english** **Sökinställningar - Hitta alla mina söktermer**	**43**
S11	S7 AND S10	45
S10	S8 OR S9	317,217
S9	TI (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*) OR AB (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*) OR KW (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*)	314,615
S8	DE "Major Depression" OR DE "Depression (Emotion)" OR DE "Treatment Resistant Depression" OR DE "Late Life Depression" OR DE "Endogenous Depression" OR DE "Seasonal Affective Disorder"	150,488
S7	S5 OR S6	197
S6	TI (tVNS OR taVNS) OR AB (tVNS OR taVNS) OR KW (tVNS OR taVNS)	81
S5	S3 AND S4	186
S4	S1 OR S2	1,612
S3	TI (transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable) OR AB (transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable) OR KW (transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable)	9,893
S2	TI VNS OR AB VNS OR KW VNS	682
S1	vagus nerve stimulation OR vagus nerve stimulations OR vagal nerve stimulation OR vagal nerve stimulations	1,530

Database: CINAHL (EBSCOhost)
Date: 22 June 2020
No. of results: 27

#	Undran	Resultat
S16	**S11 AND S14** **Utökning - Sök med relaterade ord; Sök med likvärdiga ämnesord** **Begränsa genom att Language: - english** **Sökinställningar - Hitta alla mina söktermer**	**27**
S15	S11 AND S14	27
S14	S12 OR S13	193,262
S13	TI (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*) OR AB (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*)	164,378
S12	(MH "Depression+")	121,188
S11	S6 OR S9 OR S10	188
S10	TI (OR tVNS OR taVNS) AND AB (OR tVNS OR taVNS)	2
S9	S7 AND S8	41
S8	TI (vagus nerve OR vagal nerve) OR AB (vagus nerve OR vagal nerve)	1,671
S7	(MH "Transcutaneous Electric Nerve Stimulation")	2,381
S6	S4 AND S5	178

S5	TI (transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable) OR AB (transcutaneous or non-invasive OR noninvasive OR auricular OR non-implantable OR nonimplantable)	38,796
S4	S1 OR S2 OR S3	1,561
S3	TI VNS OR AB VNS	389
S2	vagus nerve stimulation OR vagus nerve stimulations OR vagal nerve stimulation OR vagal nerve stimulations	1,249
S1	(MH "Vagal Stimulation")	782

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
18 August 2020
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 30 new records

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Reference lists

Included studies:

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Project: Transcutaneous vagus nerve stimulation in patients with depression

Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study groups; Intervention vs control	Patients (n)	Mean age years (SD)	Men (%)	Outcome variables
Hein, 2013 Germany	RCT, study 1	2 weeks	I=taVNS 15 min. once/ day + standard treatment C=sham taVNS 15 min. once/day + standard treatment	Inpatients with MDD (22)	I: 45 C:46 (12)	55% 27%	Depressive symptoms, measured with HDRS-17 (HAM-D), BDI Complications
	RCT, study 2		I=taVNS 15 min. once/twice per day + standard treatment/ C=sham taVNS 15 min. once/twice per day + standard treatment	Inpatients with MDD (15)	I: 49 (8) C: 47 (10)	14% 62%	Depressive symptoms, measured with HDRS-17 (HAM-D), BDI Complications (Standard treatment= antidepressant + CBT)
Rong, 2016 China	Cohort study	4 weeks	I=taVNS 30 min. twice a day C=sham taVNS 30 min. twice a day	Outpatients with mild to moderate MDD (160)	I: 40 (16) C: 44 (14)	25% 29%	Depressive symptoms, measured with HAM-D, SDS, Anxiety symptoms, measured with HAM-A, SAS Complications
Trevizol, 2016 Brazil	Case series	2 weeks	taVNS 30 min once/day, total of 10 sessions	Outpatients with MDD (12)	46 (9)	17%	Complications

taVNS: Transcutaneous auricular vagus nerve stimulation; MDD: Major depressive disorder; HDRS-17 (HAM-D): Hamilton Depression Rating Scale; BDI: Beck's Depression Inventory; CBT: Cognitive Behavioural Therapy; SDS: Self-rating Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; SAS: Self-rating Anxiety Scale

Project: Transcutaneous vagus nerve stimulation for treatment of depression
Appendix 3 Excluded articles

Author year	Reason for exclusion
Fang 2016	Duplicate publication of Rong 2016
Fang 2017	Duplicate publication of Rong 2016
Koenig 2019	Wrong O
Kong 2018	Duplicate publication of Rong 2016
Liu 2016	Duplicate publication of Rong 2016
Polak 2014	Wrong O and C, no safety information
Tu 2018	Duplicate publication of Rong 2016
Wang 2018	Duplicate publication of Rong 2016
Wu 2018	Systematic review
Yap 2020	Systematic review
Zhang 2016	Systematic review

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.1
Outcome variable: Depressive symptoms

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention taVNS	Control Sham taVNS				
Hein, 2013 Germany	RCT, Study 1	N=22 I=11 C=11	0	**taVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 15.4 (SD 6.8) After 2 weeks: 10.6 (SD 5.7) Δ=-4.8 (SD 6.5) **BDI** Baseline: 27.0 (SD 12.8) After 2 weeks: 14 (SD 9.5) Δ=-13.0 (SD 6.7)	**Sham taVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 20.1 (SD 6.9) After 2 weeks: 12.9 (SD 7.9) Δ=-7.2 (SD 8.1) *Between-group difference: n*s **BDI** Baseline: 31.0 (SD 10.1) After 2 weeks: 25.8 (SD 14.1) Δ=-5.2 (SD 11.7) *Between-group difference: ns (p=0.057)*	MDD patients Add-on design *taVNS vs sham taVNS protocol study 1:*15 min. once per day for 2 weeks (5 days/w) + standard treatment (antidepressant + CBT) TENS device: NET-2000 (application by the clinicians)	?	-	-
	Study 2	N=15 I=7 C=8		**taVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 18.4 (SD 6.3) After 2 weeks: 12.1 (SD 6.0) Δ=-6.3 (SD 4.0) **BDI** Baseline: 29.4 (SD 9.9) After 2 weeks: 17.4 (SD 9.6) Δ=-12.0 (SD 4.7)	**Sham tVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 15.3 (SD 8.0) After 2 weeks: 9.6 (SD 3.6) Δ=-5.9 (SD 5.2) *Between-group difference: n*s **BDI** Baseline: 28.6 (SD 12.7) After 2 weeks: 25.4 (SD 14.2) Δ=-3.2 (SD 6.4) *Between-group difference: p<0.05*	*taVNS vs sham taVNS protocol study 2:*15 min. once/twice per day for 2 weeks (5 days/w) + standard treatment (antidepressant + CBT) TENS device: NET-1000 (self-application by the patients) *Scales:* HDRS-17 scores (range: 0 – 52) < 7 absence/remission of depression 7-17 mild depression 18-24 moderate depression ≥ 25 represent severe depression			

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.1
Outcome variable: Depressive symptoms

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention taVNS	Control Sham taVNS				
	Study 1+2	N=37 I=18 C=19		**taVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 16.6 (SD 6.8) After 2 weeks: 11.2 (SD 5.9) Δ=-5.4 (SD 5.7) **BDI** Baseline: 27.9 (SD 11.8) After 2 weeks: 15.3 (SD 9.7) Δ=-12.6 (SD 6.0)	**Sham taVNS + standard treatment** **HDRS-17 (HAM-D)** Baseline: 18.1 (SD 7.8) After 2 weeks: 11.5 (SD 6.7) Δ=-6.6 (SD 7.1) *Between-group difference: 1.2* *Mann-Whitney U test:* *U= 161.1, ns* **BDI** Baseline: 30.0 (SD 11.4) After 2 weeks: 25.6 (SD 14.2) Δ=-4.4 (SD 9.9) *Between-group difference: -8.2* *Mann-Whitney U test:* *U= 265.0, p=0.004*	BDI scores (self-rating): (range: 0 – 63) 1-10 normal 11-16 Mild mood disturbance 17-20 Borderline clinical depression 21-30 Moderate depression 31-40 Severe depression > 40 Extreme depression No response or remission data *Sample-note:* Inpatients. Small sample size Short length of treatment Different antidepressant therapies			
Rong, 2016 China	Cohort study	N=160 I=91 C=69	I=7 C=15	**taVNS** **HDRS-24 (HAM-D-24)** Baseline: 25.1 (SD 7.0) Week 4: 15.2 (SD 6.3) Δ=-9.9¨ **SDS** Baseline: 61.6 (SD 9.7) Week 4: 48.3 (SD 12.0) Δ=-13.3¨	**Sham taVNS** **HDRS-24 (HAM-D-24)** Baseline: 24.4 (SD 5.5) Week 4: 20.6 (SD 5.6) Δ=-3.8 *Between-group difference (CI 95%):* *-6.1(-4.5 to -8.3), p<0.0001* **SDS** Baseline: 63.3 (SD 8.8) Week 4: 59.1 (SD 9.2) Δ=-4.2	Mild to moderate MDD patients *taVNS/sham-taVNS protocol:* 30 min. twice a day TENS device: ear vagus nerve stimulator developed by Institute of Acupuncture and Moxibustion, China Academy of Chinese Medicine Sciences and (Beijing, China) and Suzhou Medical Appliance Factory (Jiangsu Province, China). Self-application by the patients at home.	?	-	+

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.1
Outcome variable: Depressive symptoms

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention taVNS	**Control Sham taVNS**				
				Response Week 4: 27% **Remission** Week 4: 3%	*Between-group difference (CI 95%):* *-9.1 (-5.5 to -12.4) p<0.0001* **Response** Week 4: 0% *Between-group difference: p<0.0001* **Remission** Week 4: 0% *Between-group difference: n*s	*Scales:* HDRS-24 (HAM-D-24) scores: (range: 0 – 96) 0–7 normal 8–16 suggest mild depression 17–23 moderate depression scores ≥ 24 severe depression SDS scores (self-rating): (range: 20 – 80) 25-49 Normal range 50-59 Mildly depressed 60-69 Moderately depressed ≥70 Severely depressed Response definition: 50% reduction in HAM-D-24 Remission definition: HAM-D-24 score <8 *Sample-note:* Outpatients. No medication Sum data only from hospital 1 and 2 (no sham data from hospital 3) Single-blinded study Wash-out: 2 weeks			

taVNS: transcutaneous auricular vagus nerve stimulation; MDD: major depressive disorder; HDRS-17 (HAM-D) and HDRS-24 (HAM-D-24): Hamilton Depression Rating Scale; BDI: Beck's Depression Inventory; TENS: transcutaneous electrical nerve stimulation; CBT: Cognitive Behavioural Therapy; SDS: Self-rating Depression Scale;

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.2
Outcome variable: Anxiety symptoms

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention taVNS	Control Sham taVNS				
Rong, 2016 China	Cohort study	N=160 I=91 C=69	I=7 I=15	**HAM-A** Baseline: 16.4 (SD 7.1) Week 4: 10.5 (SD 6.6) Δ=-5.9 **SAS** Baseline: 51.3 (SD 9.7) Week 4: 43.5 (SD 11.0) Δ=-7.8	**HAM-A** Baseline: 14.2 (SD 5.1) Week 4: 11.3 (SD 3.8) Δ=-2.9 *Between-group difference (95% CI):* *-3.0 (-1.6 to -5.6), p<0.0001* **SAS** Baseline: 52.7 (SD 9.7) Week 4: 50.0 (SD 7.9) Δ=-2.7 *Between-group difference (95% CI): -5.1 (0.5 to -7.2)* *p=0.01*	Mild to moderate MDD outpatients *taVNS vs sham taVNS protocol:* 30 min. twice a day TENS device: ear vagus nerve stimulator developed by Institute of Acupuncture and Moxibustion, China Academy of Chinese Medicine Sciences (Beijing, China) and Suzhou Medical Appliance Factory (Jiangsu Province, China). Self-application by the patients at home. *Scales:* *HAM-A scores:* (range: 0- 56) <17 indicates mild severity 18–24 mild to moderate severity 25–30 moderate to severe SAS scores (self-rating): (range: 20 – 80) 20-44 Normal range 45-59 Mild to moderate anxiety 60-74 Marked to severe anxiety 75-80 Extreme anxiety *Sample-note:* Outpatients. No medication. Sum data only from hospital 1 and 2 (no sham data from hospital 3) Single-blinded study, Wash-out of antidepressant medication prior to study treatment: 2 weeks	?	-	?

taVNS: transcutaneous auricular vagus nerve stimulation; MDD: major depressive disorder; CBT: Cognitive Behavioural Therapy; HAM-A: Hamilton Anxiety Rating Scale; SAS: Self-rating Anxiety Scale

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention taVNS	Control Sham taVNS				
Hein, 2013 Germany	RCT	N=37 I=18 C=19	0	**taVNS + standard treatment** No reported side effects/complications	**Sham taVNS + standard treatment** No reported side effects/complications	MDD patients Add-on design *taVNS vs sham taVNS protocol study 1* 15 min. once per day for 2 weeks (5 days/w) + standard treatment (antidepressant + CBT) TENS device: NET-2000 (application by the clinicians) *taVNS vs sham taVNS protocol study 2* 15 min. once/twice per day for 2 weeks (5 days/w) + standard treatment (antidepressant + CBT) TENS device: NET-1000 (self-application by the patients) *Sample-note:* Inpatients. Small sample size Short treatment duration Different antidepressant therapies	?	-	-
Rong, 2016 China	Cohort study	N=160 I=91 C=69	I=7 C=15	**taVNS** Worsening of tinnitus, n=2 (fully recovered after stopping taVNS)	**Sham taVNS** Worsening of tinnitus, n=3 (fully recovered after stopping sham taVNS)	Mild to moderate MDD outpatients *taVNS vs sham taVNS protocol:* 30 min. twice a day TENS device: ear vagus nerve stimulator developed by Institute of Acupuncture and Moxibustion, (Beijing, China) and Suzhou Medical Appliance Factory	?	-	+

Project: Transcutaneous vagus nerve stimulation in patients with depression
Appendix 4.3
Outcome variable: Complications

* + No or minor problems
? Some problems
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Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **taVNS**	**Control** **Sham taVNS**				
						(Jiangsu Province, China). Sself-application by the patients at home. *Sample-note:* Outpatients. No medication Sum data only from hospital 1 and 2 (no sham data from hospital 3) Single-blinded study Wash-out: 2 weeks			
Trevizol, 2016 Brazil	Case series	N=12	N=0	**taVNS** Mild parestesia underneath the electrodes under stimulation, n=12 Severe adverse effects, n=0 Mild to moderate diurnal sleepiness, n=10 Mild to moderate tension headaches (no need for medication), n=6 Mild to moderate nausea, n=4 Side effects at 1month follow-up, n=0	-	MDD patients *taVNS protocol:* 30 min/day x 10 sessions Electrodes placed bilaterally over the mastoid process area *Device:* Ibramed Neurodyn II *Sample-note:* Outpatients			

taVNS: transcutaneous auricular vagus nerve stimulation; MDD: major depressive disorder; CBT: Cognitive Behavioural Therapy

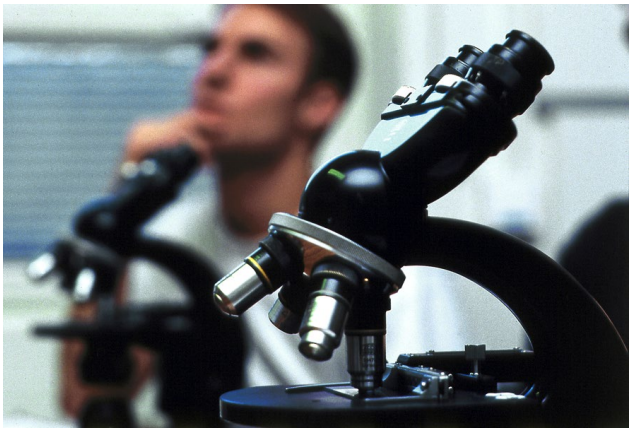
Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [ ] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [x] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

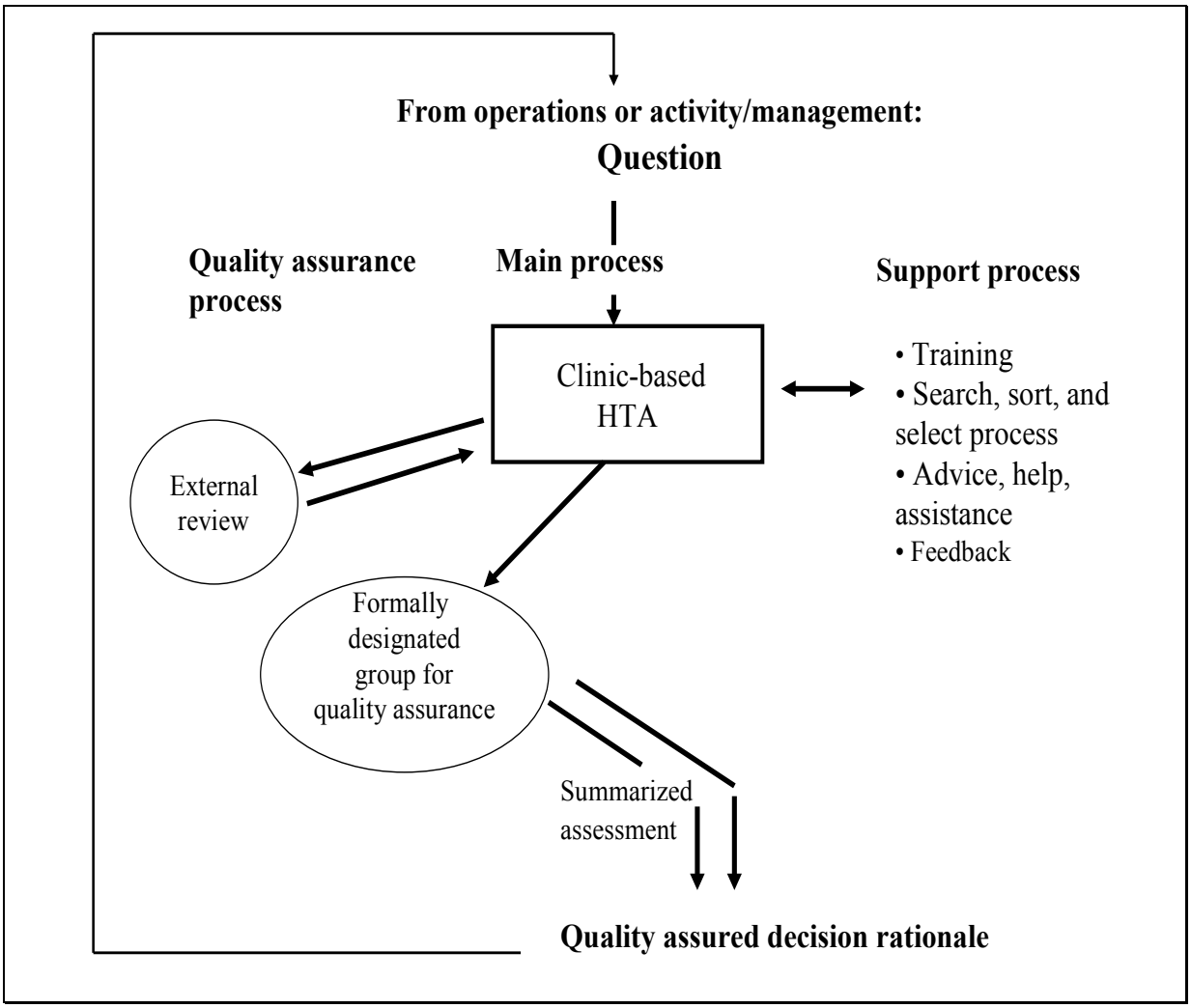
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/htacentrum