Artikel online veröffentlicht: 23.05.2022



# Vagus Nerve Stimulation for Conservative Therapy-Refractive Epilepsy and Depression

OPEN ACCESS

Authors
H Möbius[1, 2], H J Welkoborsky[1, 2]

Affiliations
1 Department of Oto-Rhino-Laryngology, Head & Neck Surgery, KRH Klinikum Nordstadt, Hannover Germany
2 Department of Oto-Rhino-Laryngology, Children's Hospital auf der Bult, Hannover, Germany

Key words
Epilepsy; depression; vagus nerve stimulation; responsive vagal nerve stimulation; transcutaneous vagal nerve stimulation; quality of life; biomarker; mechanism of action

Bibliography
Laryngo-Rhino-Otol 2022; 101: S114–S143
DOI 10.1055/a-1660-5591
ISSN 0935-8943
© 2022. Thieme. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commecial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/)
Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Hartmut Möbius
Department of Oto-Rhino-Laryngology
Head & Neck Surgery
Klinikum Nordstadt der KRH
Haltenhoffstr. 41
30167 Hannover
Germany
hartmut.moebius@krh.de

## ABSTRACT/CONCLUSION

Numerous studies confirm that vagus nerve stimulation (VNS) is an efficient, indirect neuromodulatory therapy with intermittently applied electrical current used for epilepsy that either cannot be treated by epilepsy surgery or is therapy-refractory. It is effective in drug therapy-refractory depressions as well. VNS is an established, evidence-based and in the long-term cost-effective therapy in an interdisciplinary overall concept. Long-term data on the safety and tolerance of the method are available despite the heterogeneity of the patient populations. Stimulation-related side effects like hoarseness, paresthesia, cough or dyspnea depend on the stimulation strength and often decrease with continuing therapy duration in the following years. Stimulation-related side effects of VNS can be well influenced by modifying the stimulation parameters. Overall, the invasive vagus nerve stimulation may be considered as a safe and well-tolerated therapy option.

Antiepileptic and antidepressant as well as positive cognitive effects could be proven using invasive and transcutaneous vagus nerve stimulation. In contrast to drugs, VNS has no negative effect on cognition. In many cases, an improvement of the quality of life is possible.

iVNS therapy has a low probability of complete seizure-freedom in cases of focal and genetically generalized epilepsy. It must be considered as palliative therapy, which means that it does not lead to healing and requires the continuation of specific medication. The functional principle is a general reduction of the neuronal excitability. This effect is achieved by a slow increase of the effectiveness sometimes over several years. Responders are those patients who experience a 50 % reduction of the seizure incidence. Some studies even reveal seizure-freedom in 20 % of the cases. Currently, it is not possible to differentiate between potential responders and non-responders prior to therapy/implantation.

The current technical developments of the iVNS generators of the new generation like closed-loop system (cardiac-based seizure detection, CBSD) reduce also the risk for SUDEP (sudden unexpected death in epilepsy patients), a very rare, lethal complication of epilepsies, beside the seizure severity.

iVNS may deteriorate an existing sleep apnea syndrome and therefore requires possible therapy interruption during nighttime (day-night programming or magnet use) beside the close cooperation with sleep physicians.

The evaluation of the numerous iVNS trials of the past two decades showed multiple positive effects on other immunological, cardiological, and gastroenterological diseases so that additional therapy indications may be expected depending on future study results. Currently, the vagus nerve stimulation is in the focus of research in the disciplines of psychology, immunology, cardiology as well as pain and plasticity research with the desired potential of future medical application.

Beside invasive vagus nerve stimulation with implantation of an IPG and an electrode, also devices for transdermal and thus non-invasive vagus nerve stimulation have been developed

during the last years. According to the data that are currently available, they are less effective with regard to the reduction of the seizure severity and duration in cases of therapy-refractory epilepsy and slightly less effective regarding the improvement of depression symptoms. In this context, studies are missing that confirm high evidence of effectiveness. The same applies to for other indications like tinnitus, cephalgia, gastrointestinal complaints etc. In contrast to implanted iVNS therapy systems another disadvantage of transcutaneous vagus nerve stimulation is the stimulator which has to be applied actively by the patients and is not permanently active. So they are only intermittently active; furthermore, the therapy adherence is uncertain.

**Contents**



## 1. Introduction

Epilepsy and depression are the most frequent neurologic-psychiatric diseases. Worldwide, about 50 million people suffer from epilepsy [1]. Every person has a life-time risk of 8–10 % to experience an epileptic seizure [2]. Every year, 50–100 of 100,000 people are newly diagnosed with epilepsy or an epileptic syndrome [3]. According to the classification of the International League Against Epilepsy (ILAE), epileptic seizures are classified into focal and generalized seizures and seizure of unknown origin [4, 5].

The annual incidence of depression amounts to 1–2 patients per 100 persons. The risk to experience depression in life (life-time prevalence) amounts to 16–20 % [6–8]. The incidence of monopolar depression in the general population is estimated to 7.7 % in an interval of 12 months, the 12-months prevalence for major depression to 6 %, and for dysthymia to 2 %. In Germany, the number of affected people amounts to about 6.2 million people who are diagnosed with monopolar depression in an interval of 12 months [9].

The treatment of epilepsy and depression is based on the current guidelines. Different therapeutic approaches exist and their central components are drug-related mono- or combination therapies.

In the context of multilevel therapy concepts the option of surgery is available for conservatively therapy refractive courses of epilepsy and depression. According to the current S3 guideline/national disease management guideline on monopolar depression [9] as well as the S1 guideline on first epileptic seizure and epilepsies in adults [10] (approval of the following S2k guideline applied for December 31, 2021), the vagus nerve stimulation is mentioned as non-drug somatic therapy procedure, which is a neuromodulatory therapy consisting of intermittent electrical stimulation of the left vagal nerve by means of a programmable pulse generator [11]. The S3 guideline on the treatment of depressive disorders in children and adolescents from 2013 is currently being revised.

Depending on the etiology of depression, non-drug somatic therapy procedures include electroconvulsive therapy (ECT), sleep restriction therapy, phototherapy, physical exercise, repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) [9] in accordance to the respective guideline.

According to the current ILAE definition, pharmaco-resistant epilepsy is diagnosed when two independent attempts of antiepileptic drug applications have been performed without any success despite adequate dosage and duration in mono- and/or combination therapy. This definition applies for about one third of all epilepsy patients [12]. From a surgical point of view, deep brain stimulation (DBS) and vagus nerve stimulation are available beside resective and non-resective surgery techniques.

While the last-mentioned interventions belong to the field of neurosurgery, the implantation of a vagus nerve stimulator is meanwhile included in the clinical routine of large ENT surgery centers. The treatment with an implantable vagus nerve stimulator (VNS Therapy) is always an interdisciplinary approach. The ENT surgeon is responsible for the surgical part, the neurologist and/or psychiatrist cares for the fitting of the IPG (implantable pulse generator) and for therapy monitoring. Further, the indication for implantation of a vagus nerve stimulator is generally made by the treating neurologist or psychiatrist.

In Germany, currently only one implantable system is available, which is called VNS Therapy manufactured by LivaNova Deutschland GmbH, Munich, Germany.

For meanwhile 30 years, VNS Therapy is approved in many countries of the world for additional treatment of epilepsy and depression and has been applied since then in more than 130,000 patients (status of August 2021).

## 2. History of vagus nerve stimulation

Since the end of the 19th century, neuroscientists have tried to develop methods for the stimulation of the brain. In 1882, the American neurologist James Corning presented a procedure called "carotid fork" for treatment of seizures by means of mechanical compression of the common carotid arteries since at that time assumption prevailed that disorders of the cerebral blood flow were the reason for epilepsy. Later, Corning combined this method even with transcutaneous electrical stimulation of the vagus nerve [13]. In the middle of the 20th century, numerous animal experimental investigations were performed. In 1952, Zanchetti and co-workers discovered by means of epilepsy models in cats that vagus nerve stimulation may block strychnine-induced epileptic spikes [14]. Further animal experiments with cats, dogs, and monkeys showed basic correlations between vagus nerve stimulation and EEG alterations as well as their influence on seizures [15, 16].

The knowledge gained from the multitude of animal experiments regarding the effect of vagus nerve stimulation and the induced changes of cerebral activities led to animal experiments with the objective to specifically interrupt seizures via vagus nerve stimulation [17–19].

In 1992, Zabara observed that experimentally induced seizures in dogs could be interrupted by VNS [20]. The detection of the anticonvulsive effect in promising preclinical trials led to the further development of VNS for clinical application of vagus nerve stimulation as treatment option for patients with therapy-refractory epilepsy. It was first in 1988 that Penry and Dean [21], Rutecki [22], and Uthman [23] introduced the therapeutic application of VNS in the context of the treatment of epilepsy patients.

Since the mid-1990s, VNS has been applied for the treatment of therapy-refractory epilepsies in Europe (1994) and in the USA (1997). Since the beginning of the 2000s, VNS has been applied in the USA, Canada, and Europe (in Germany since 2001) also for treatment of depression [31, 32].

In 2015, vagus nerve stimulation was approved in Europe for the therapy of chronic heart failure (CHF). In a trial with 60 heart failure patients, a significant improvement of some cardiac parameters could be revealed [33].

Outside the USA, the invasive vagus nerve stimulation (VNS Therapy System, LivaNova PLC) is currently a certified additional therapy of epilepsy in order to reduce the incidence of seizures in pharmaco-resistant patients with focal seizures with or without secondary generalization or in patients with generalized seizures [34, 35]. There is no age limit defined for this kind of treatment.

In the context of depression, the VNS Therapy System is indicated for treatment of chronic or recurrent depressions in patients who are in a therapy-refractory or intolerant episode of a major depression [35].

In contrast to interventions in the context of resective epilepsy surgery, stimulation therapy with invasive nerve stimulation has the great advantage of reversibility [5].

For treatment of epilepsy and depression by means of vagus nerve stimulation, currently (status of August 2021) more than 1,300 peer-reviewed publications are available in the databases (▶ **Table 1**), among them 12 basic research/approval studies.

Beside the invasive form of vagus nerve stimulation (VNS Therapy), non-invasive transcutaneous stimulation procedures have been developed. In 2010, the first transcutaneous vagus nerve stimulators (tVNS) were approved in Europe for application in the area of the auricle (auricular branch), first for therapy of epilepsy and depression [28], since 2012, it has also been approved for pain therapy [36].

## 3. Anatomical basics of the vagus nerve

The vagus nerve (VN), also called tenth cranial nerve or CN X, actually comprises two nerves (the right and the left one) and is the longest cranial nerve running from the head to the abdomen. Beside somato- and viscero-efferent (= parasympathetic), it also has somato- and viscero-afferent fibers as well as sensory fibers innervating the posterior part of the tongue [37]. Single afferent sensitive fibers originate from the concha of the ear [38]. The vagus

**Milestones of implantation of vagus nerve stimulators:**

| | |
|---|---|
| 1988 | First implantation in epilepsy patients by J. Kiffin Penry; Bowman Gray School of Medicine (North Carolina, USA) [21] |
| 1988–1996 | Study program, epilepsy (E-01–E-05; 454 patients) [24] |
| 1994 | CE certification for epilepsy |
| 1997 | FDA approval for epilepsy |
| 2000 | Pilot study, epilepsy (Early Observation Mood Improvement) [25] |
| 2000 | Study program, depression (D-01 & D-03) [26–28] |
| 2001 | CE certification for depression (Europe & Canada) |
| 2005 | FDA approval for depression |
| 2007 | Further clinical trials, depression (D21; D-23; Medicare) [29–30] |
| Since 2007 | Commercialization of "VNS for depression" worldwide |

▶ **Table 1** Number of published papers on VNS in the context of depression and therapy-refractory epilepsy (source: www.ncbi.nih.nlm.gov, retrieved in August 2021).

| Primary focus | Number of publications |
|---|---|
| Effectiveness | >500 |
| Safety | >150 |
| Handling | >30 |
| Economics | >15 |
| Mechanism of action | >250 |
| Review articles | >50 |

nerve is the main parasympathetic nerve of the autonomous nervous system [39].

The vagus nerve innervates the following organs: heart, airways and lung, esophagus, stomach, liver, pancreas, gastro-intestinal tract, and kidneys [40–43].

The vagus nerve exits from the posterior lateral sulcus of the medulla oblongata between the olive and the fasciculus cuneatus/graciles [44] and leaves the skull together with the glossopharyngeal nerve (CN IX) and the accessory nerve (CN XI) through the jugular foramen [37]. Four cranial nerve nuclei belong to it: the solitary tractus nucleus, the spinal trigeminal nucleus, the dorsal nucleus of vagus nerve, and the nucleus ambiguous [45]. In the cervical area, the vagus nerve is located deep in the carotid bifurcation between the carotid artery and the internal jugular vein and runs caudally on the right and the left side of the trachea with following complex abdomino-pelvine course [46].

Cervically, the nerve includes about 80 % of afferent and 20 % of efferent fibers [47]. The vagus nerve is a mixed nerve and in the cervical area, it consists of about 10–15 single nerve fiber bundles [48–50].

Due to systematic functional investigations, the neurons of the vagus nerve could be classified into A, B, and C fibers [51]. The A fibers (including Aα, Aβ und Aδ) consist of myelinated somatic, afferent and efferent neurons with diameters of 1–22 µm and line speeds of 5–120 m/s. The B fibers are moderately myelinated, efferent and mainly preganglionic autonomous fibers with diameters of 3 µm and line speeds of 3–15 m/s. The myelinated A and B fibers represent about 20 % of the vagus nerve neurons. The remaining about 80 % of unmyelinated C fibers are definitely not involved in the anticonvulsive effect of VNS therapy [52] but are responsible for pain transmission [5].

The sensory afferent fibers with cell bodies in the inferior ganglion (formerly: nodose ganglion) connect in the nucleus tractus solitarius (NTS) and project to different brain regions [53–57] (▶ **Figs. 1** and ▶ **2**). They transmit pain, temperature, and tactile perceptions [58, 59]. Non painful visceral stimuli are transmitted via parasympathetic fibers [60], while visceral pain stimuli are transmitted via sympathetic fibers [61].

Incoming sensory information of the NTS are transmitted via three main pathways to the other parts of the brain: 1) an autonomous feedback loop, 2) direct projections to the reticular formation in the medulla oblongata, and 3) ascending projections over the parabrachial nucleus (PB) and locus coeruleus (LC) to the forebrain [63, 64]. Due to the multiple parabrachial reflex projections, the NTS may influence respiratory activities as well as pain modulation.

Via projections of the NTS to the amygdala, the NTS has direct access to the amygdala-hippocampus-entorhinal cortex of the limbic system, which is the site that generates most frequently complex partial seizures [5].

The parabrachial nucleus (PB) and locus coeruleus (LC) project directly to key structures of the limbic system that play a significant role in the processing of affects and the emotional evaluation of information (hypothalamus, certain thalamic regions, island regions, orbitofrontal and prefrontal cortex, amygdala, and terminal stria) [66]. The functional significance of these connections of the vagus nerve to the brainstem and the limbic system have been described in multiple publications [67–71].

The vagus nerve contains somatic and visceral afferences as well as efferences. The **efferent** fibers mainly originate from the dorsal nucleus of the vagus nerve located in the medulla oblongata [72] and the ambiguous nucleus. They are responsible for the parasympathetic autonomous innervation of most thoracic and abdominal organs, for the motor innervation of larynx and pharynx [31, 44] as well as the vocal cords [72]. The pathway vagus nerve-NTS-parabrachial nuclei is further involved in the processing of pulmonary information so that altered vagal sensory input into this system during vagus nerve stimulation sometimes leads to subjectively perceived dyspnea, however, without measurable changes of pulmonary parameters [5].

The vagal parasympathetic efferences lead to neurons that are found in the parasympathetic ganglia. These ganglia are located near the target organs. The vagus nerves are asymmetric with regard to cardiac innervation. The left vagus nerve contains more parasympathetic fibers predominantly innervating the ventricles and the AV nodes; and the right vagus nerve contains more fibers that innervate mainly the cardiac atrium [72] as well as the sinus node. Different animal experimental studies confirmed the stronger cardiac effect on the right side [73, 74].

Therefore, the use of the left vagus nerve is preferred over the right one in the context of invasive vagus nerve stimulation in order to avoid cardiac side effects like arrhythmia [31, 44].

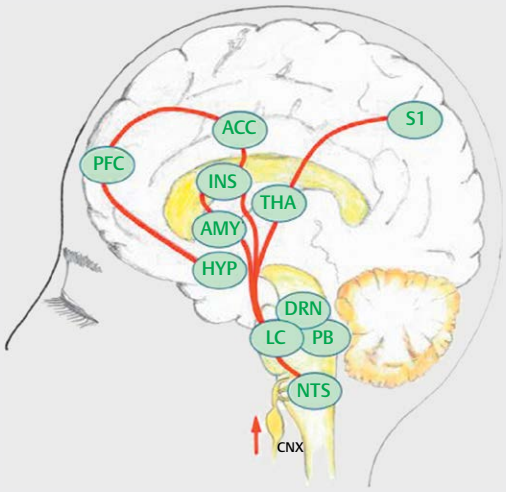
The **afferent** fibers mainly originate from two parasympathetic ganglia near the skull base [72]. They transmit visceral information to the nucleus tractus solitarii (NTS) – and afterwards to the locus coeruleus, hypothalamus, thalamus, amygdala, and insula cortex – as well as other regions of the brain such as the spinal nucleus of the trigeminal nerve, the area postrema, and the medial reticular formation of the medulla oblongata [31, 44], the dorsal nucleus of the vagus nerve, and the ambiguous nucleus [72].

The auricular branch of the vagus nerve (also called Arnold´s nerve) is responsible for the sensitive innervation of parts of the auricle and the posterior wall of the auditory canal. This is important for the therapy approach of non-invasive VNS. Also, Arnold's reflex, an involuntary cough reflex, is triggered by stimulation of the auricular branch of the vagus nerve for example in cases of mechanical manipulation [75]. Arnold's nerve runs from the superior ganglion above the jugular foramen through a bony ostium in the petrous bone and together with the facial nerve in the canal of the facial nerve. It exits from the tympanomastoid fissure above the styloid foramen and splits into fibers for the posterior wall of the auditory canal and for parts of the auricle (see chapter 5.2) [75–77]. Centrally, via the superior ganglion, the auricular branch of the vagus nerve is connected to the brainstem and in particular to the NTS [78].

## 4. Neurophysiological basics of the effect mechanism of vagus nerve stimulation

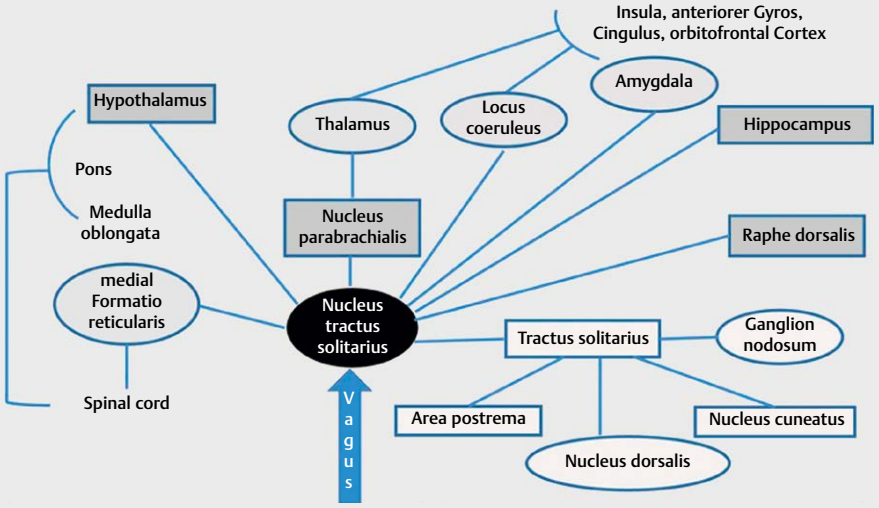
In the synapses of the vagal afferences, excitatory (glutamate and aspartate) and inhibitory (GABA) neurotransmitters are found like acetylcholine and a large number of neuropeptides.

Via the nucleus tractus solitarius, the vagal afferences are projected to noradrenergic as well as serotonergic neuromodulatory systems in the brain and spinal cord. In the locus coeruleus the high-




ACC = anterior cingulate cortex
AMY = amygdala
DRN = dorsal raphae nuclei
HYP = hypothalamus
INS = insula
LC = locus coeruleus
NTS = nucleus tractus solitarii
PB = parabrachial nucleus
PFC = prefrontal cortex
S1 = primary somatosensory cortex
THA = thalamus
CNX = vagus nerve

▶ **Fig. 1** Anatomical connections of the vagus nerve 1: Courtesy of S. Fetzer, LivaNova 2021, modified according to Hachem et al. 2018 [62].




▶ **Fig. 2** Anatomical connections of the vagus nerve 2. Drawn by Möbius in 2021 according to Rush et al. 2002 [65].

est density of noradrenergic neurons in the brain is found. Thus, the LC is responsible for a wide noradrenergic innervation of the entire cortex, diencephalon, and many other cerebral structures. In contrast to the morphologically clearly defined LC, the raphe nuclei in the reticular formation are diffusely distributed. They represent the main source for serotonin and are responsible for an extensive serotonergic innervation of the whole cortex, diencephalon, and other cerebral structures [5].

Interactions between vagus nerve and locus coeruleus or vagus nerve and raphe nuclei are potentially congruent to the mechanism of invasive vagus nerve stimulation because noradrenaline, adrenaline, and serotonin have, among others, anticonvulsive and antidepressant effects [5].

Walker and colleagues revealed experimentally the central role of the NTS in the anticonvulsive effect of invasive VNS. The increase of GABA and the decrease of the glutamate concentration with subsequently reduced activity in the NTS had an anticonvulsive effect [79]. In a rat model of limbic seizures, Raedt and colleagues confirmed that the anticonvulsive effect of VNS is due to the increased release of noradrenaline in the hippocampus; a correlation was found between the noradrenaline concentration and the anticonvulsive effect [38, 80].

The affect-modulating function of the limbic system is a field of major research in the indication of depression. The physiological impact of the vagus nerve stimulation on this and higher cerebral structures was investigated frequently by means of modern ima-

ging procedures (fMRI, PET, SPECT, MEG) making the effect mechanism of this therapy more and more transparent [81–85].

In summary, noradrenaline, adrenaline, and serotonin seem to have also anticonvulsive and mood-lifting effects.

Two of the main functions of the vagus nerve are speaking and swallowing, mediated via specific visceral efferent fibers originating from the ambiguous nucleus [58, 59]. The recurrent laryngeal nerve also includes such specific fibers and innervates the adductors and abductors of the larynx [86], which is necessary to form rough sounds in differentiated language [59]. This fact might explain voice irritations during the active stimulation phase of VNS therapy. Somatosensory thalamic neurons project to the inferior post-central gyrus and the inferior parietal flap. Vago-trigemino-thalamocortical processes control laryngeal and pharyngeal sensations [5].

Furthermore, the vagus nerve is an important part of combating chronic inflammatory processes in the body. There is a bidirectional communication between the brain and the gastrointestinal tract. The anti-inflammatory role of the vagus nerve is performed either due to vagal afferences, by means of the hypothalamus-pituitary gland-adrenals axis (stress axis) or vagal efferences that aim at the cholinergic anti-inflammatory pathway and block the release of inflammation mediators by macrophages like the tumor necrosis factor (TNFα). Neuroimmunology is a rather young, ambitious research field for the application of VNS Therapy [87–89]. All these vagal functions lead to the following model of vagus nerve stimulation (see ▶ **Fig. 3**).

An improved daytime vigilance by means of VNS is achieved by an improved reticular activating system function even if the mechanism of change due to invasive vagus nerve stimulation is still not exactly known [72].

## 5. Types of vagus nerve stimulation

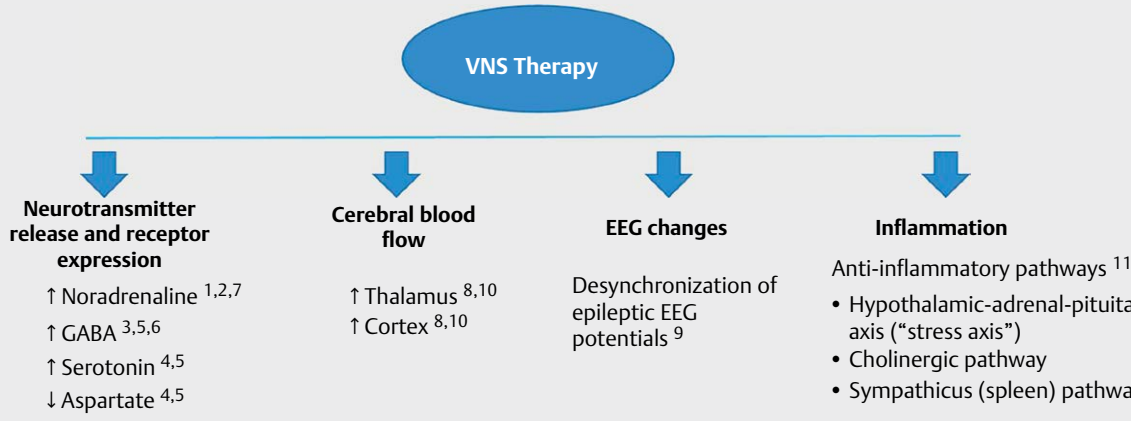
As non-drug, somatic therapy procedure, vagus nerve stimulation is a neuromodulatory treatment that consists of intermitting electrical stimulation of the left vagus nerve by means of a (programmable) pulse generator.

Generally, the types of vagus nerve stimulators may be classified as follows:

- Vagus nerve stimulator that has to be implanted surgically (invasive vagus nerve stimulation, iVNS or VNS Therapy)
- Non-invasive transcutaneous auricular or cervical vagus nerve stimulation (taVNS and tcVNS)

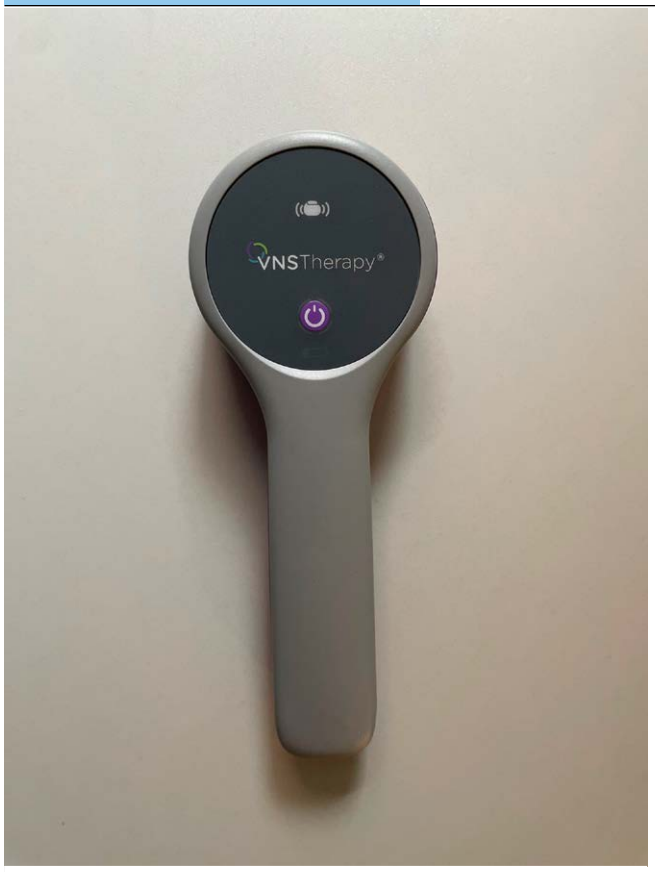
### 5.1. Invasive vagus nerve stimulation (iVNS)

In the context of invasive VNS Therapy (LivaNova PLC Company), the battery-operated generator (model Sentiva) and the stimulation electrode are implanted surgically in a procedure which takes about 1–2 h. After wound healing (about 15 days), the electrical stimulation (and thus therapy) is started. Hereby, the nerve fibers of the left vagus nerve leading to the brain are depolarized by means of weak electrical impulses and action potentials are trigge-

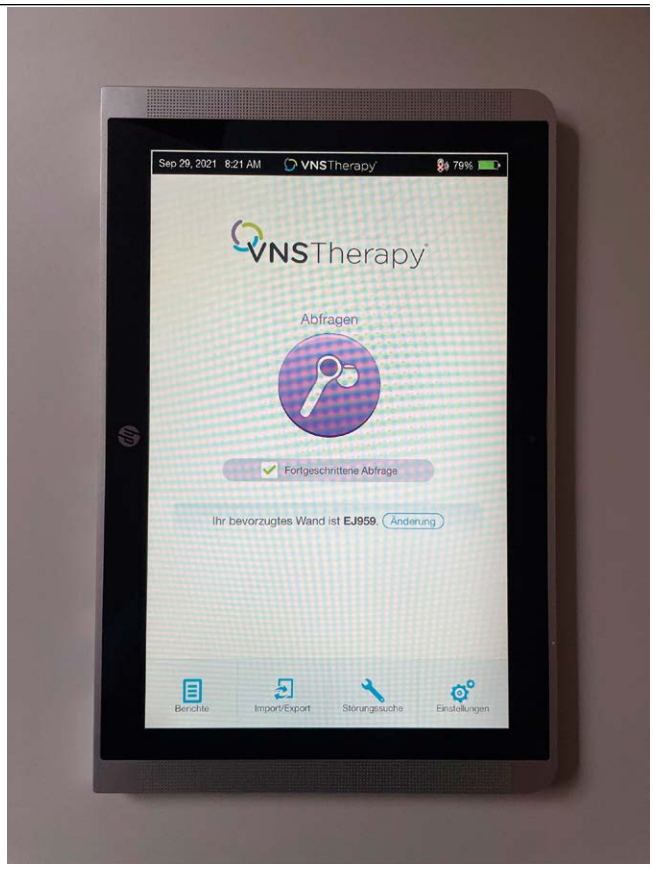



1. Roosevelt RW, Smith DC, Clough RW et al. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. Brain Res 2006;1119 (1):124-32. 2. Hassert DL, Miyashita T, Williams CL. The Effects of Peripheral Vagal Nerve Stimulation at a Memory-Modulating Intensity on Norepinephrine Output in the Basolateral Amygdala. Behavioral Neuroscience 2004; 118 (1 ):79-88. 3. Woodbury DM, Woodbury JW. Effects of Vagal Stimulation on Experimentally Induced Seizures in Rats. Epilepsia 1990; 31(2):7-19. 4. Hammond BM, et al. Neurochemical effects of vagus nerve stimulation in humans. Brain Research 1992; 583(1-2):300-3. 5. Ben-Menachem E, Hamberger A et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res 1995; 20(3):221-7.6. Marrosu F, Serra A et al. Correlation between $GABA_A$ receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. Epilepsy Res 2003; 55(1-2):59-70. 7. Krahl SE, Clark KB et al. Locus Coeruleus Lesions Suppress the Seizure-Attenuating Effects of Vagus Nerve Stimulation Epilepsia. 1998; 39(7):709-14. 8.Henry TR, Bakay RAE et al. Brain Blood-flow Alterations Induced by Therapeutic Vagus Nerve Stimulation in Partial Epilepsy: II. Prolonged Effects at High and Low Levels of Stimulation Epilepsia. 2004;45(9):1064-70. 9.Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol. 2001;18:434-41. 10.Vonck K et al. Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study. Seizure 2008; 17(8):699-706 11 . Bonaz et al. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol 2016; 20: 5781-5790.

▶ **Fig. 3** Effect model of vagus nerve stimulation. Drawing: Möbius 2021.




▶ **Fig. 4** Wand model 2000.




▶ **Fig. 5** Programmer model 3000.

▶ **Fig. 6** Magnet for VNS Therapy. (Fig. 4–6 privat. H. Möbius 2021)

red afterwards. Via the afferences, this procedure leads to multiple physiological and structural effects in the brain without influencing the inner organs. The latter would only be possible with clearly higher amperage than the VNS generator can technically produce and would require a specific polarity of the stimulation electrodes.

Postoperatively, the generator is connected externally with a computer (programmer) and a programming unit held in front of the chest ("wand") and programmed patient-specifically by the physician (▶ **Figs. 4** and ▶ **5**).

Beyond regular stimulation impulses which are automatically applied by the VNS Therapy generator, it is also possible for epilepsy patients to externally activate the generator with a particular VNS Therapy magnet if needed (e. g. when the patient feels an epileptic aura). The patient passes a magnet (▶ **Fig. 6**) over the impulsor. In this way it is possible for epilepsy patients and family or caring staff to avoid, shorten, or alleviate the onset of a seizure. Furthermore, it is possible to stop stimulation by placing the magnet on the IPG, for example in cases of undesired side effects [90].

### 5.1.1. Surgical technique

The implantation is performed under general anesthesia on the left cervical side in supine position. The application of perioperative antibiotic prophylaxis (single shot) is obligatory. The incision is per-

formed with observation of the skin tension lines (RSTL) and ideally on the level of the cricoid cartilage/anterior edge of the sternocleidomastoid muscle (▶ **Fig. 7**).

With preservation of the cervical vessel sheath, the bipolar electrode is placed around the cervical part of the vagus nerve at the level of the fifth to sixth cervical vertebras. In this region, it may be expected that the connection of the electrode contacts is performed caudally to the superior and inferior cervical cardiac branches of vagus nerve. The course of the electrodes is fixed with threads forming loops (▶ **Figs. 8** and ▶ **9**). The use of a bipolar nerve stimulation device or an intraoperative neuromonitoring is recommended, at the end of surgery, the regular recurrent response at the larynx (via the inferior laryngeal nerve) can be measured after final vagal nerve stimulation proximally to the electrode connection.

Afterwards, the impulse generator is implanted and fixed with threads below the left clavicula on the fascia of the major pectoralis muscle. The electrode and the impulse generator are interconnected via a subcutaneous tunnel (▶ **Figs. 10** and ▶ **11**).

During surgery, the VNS Therapy generator is tested by means of the described programming system (impedance test). After 15 days, VNS Therapy is started with a stimulation intensity of 0.25 milliampere (mA) (see chapter 5.1.4). As of this time, the vagus nerve is electrically stimulated and activated in regular intervals (e. g. every 5 minutes for 30 seconds). The used amperages are very low (0.25–0.3 mA) and are set patient-specifically (dose increase).

On the first or second postoperative day, radiographic control of the implant position is performed routinely (▶ **Fig. 12**).

If the generator battery turns low after about 6–10 years, depending on the stimulation parameters, (only) the VNS generator is exchanged in another surgical intervention that takes about one hour.

### 5.1.2. Contraindications

Contraindications of VNS implantation that have to be taken into consideration are the condition after left-sided vagotomy, treatment with therapeutic ultrasound as well as special electrotherapies where the body is exposed to current or energy flow (e. g. hydroelectric bath, TENS, therapeutic ultrasound etc.). **Note: The use of diagnostic ultrasound is always possible!** Regarding MRI suitability, see chapter 9.1.

Regarding the patients' age at the time of implantation, there is no limitation according to the manufacturer's recommendations in Germany and Europe.

Known allergies concerning implant materials (e. g. titanium, polyurethanes, silicone) and pre-existing severe cardiopulmonary or general anesthesiological contraindications are limiting factors of the implantation and have to be evaluated in an interdisciplinary expert board. The VNS Therapy system does not contain any natural latex.

In cases of multiple drug resistance microorganism (MDR) like MRSA, treatment according to the current hygienic concepts has to be performed previously in order to minimize the risk of postoperative wound infection with consecutive transplant colonization.

Condition after radiotherapy in the planned surgical area is no contraindication. Furthermore, there is no limitation of potentially required radiotherapy in the VNS implantation area for patients with already implanted VNS. However, the manufacturer indicates that cumulated X-ray might generally damage microelectronics.

In the context of later surgeries, the use of monopolar coagulation above the implantation area should be avoided. It is recommended to use bipolar electrocautery. However, if the use of monopolar coagulation is obligatory, attention must be paid that the current vector (plus to minus) does not run through the VNS Therapy generator, which might damage the electronics and lead consequently to revision.

### 5.1.3. Possible side effects and risks

**Surgery-related** and stimulation-related risks and side effects must be differentiated.

The implantation is associated with justifiable low risks and side effects compared to other epilepsy surgeries. Operative side effects like bleeding, postoperative bleeding, wound infection (3–6 % of the patients) [91], and intraoperative trauma at the structures of the surgery site can mostly be avoided if the usual standards are observed. The same is valid for intraoperative cerebrovascular complications in the context of underlying arteriosclerotic disease of the carotid arteries. A possibly increased anesthetic risk must be discussed with regard to previous polypharmacy (simultaneous intake of multiple antiepileptic drugs).

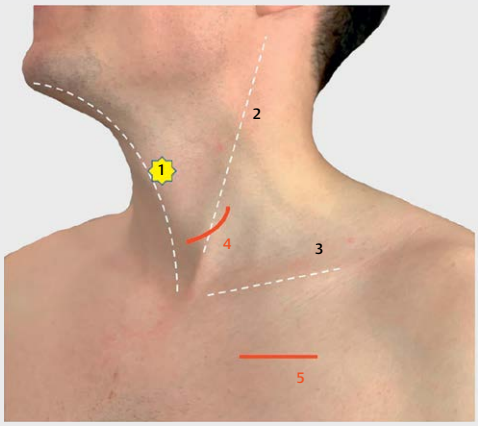
Rarely, protracted wound infection leads to explantation of the devices [92]. Some studies reveal a rate of 4–6 % of postoperative infections as well as 1–5.6 % vocal fold paresis that decreased with improved surgery techniques [93].

A rare intraoperative side effect in the context of perioperative impedance testing is the occurrence of bradycardia or asystole [94, 95]. Testing is performed under strict cardiovascular monitoring and intervention standby of anesthesiologists. The reason for the intraoperative occurrence of asystole might be: failed placing of the electrode, indirect stimulation of the cervical cardiac nerves, technical failure of the stimulator, polarity inversion by the surgeon, or specific reactions of the patient [96].

Case reports describe the occurrence of cardiac syncopes even after longer therapy durations of stimulation with interruption after switching off the vagus nerve stimulation [97]. There might possibly be an estimated number of unknown cases with cardiac symptoms in epilepsy patients because loss of consciousness in these patients is often explained by the occurrence of epileptic seizures [32].

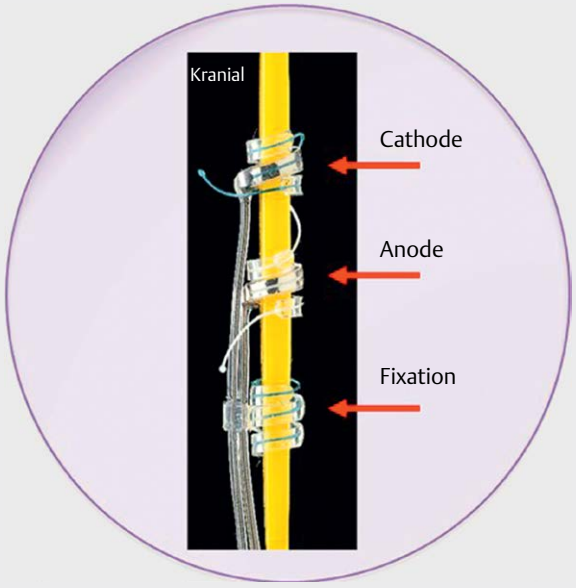
Rarely, the therapy is interrupted due to an electrode defect (cable break) caused by intensive movements or local trauma [98, 99]. The best prophylaxis for migration of the generator in the graft site (so-called twiddler) with subsequent change of the electrode position is the initially consequent fixation of the IPG with non-resorbable threads to the pectoralis muscle fascia during implantation. Even the risk of cable break or dislocation of the electrodes in the neck area can be minimized by consequent laying and fixing of the relief loop by means of non-resorbable thread material.

The most frequently observed **stimulation-related side effects** are hoarseness, cough, or the sensation of dyspnea during the short electrical stimulation phases. More rarely, breathing and swallowing disorders, sore throat, and headaches are reported. In nearly all patients, these side effects decrease in the further course

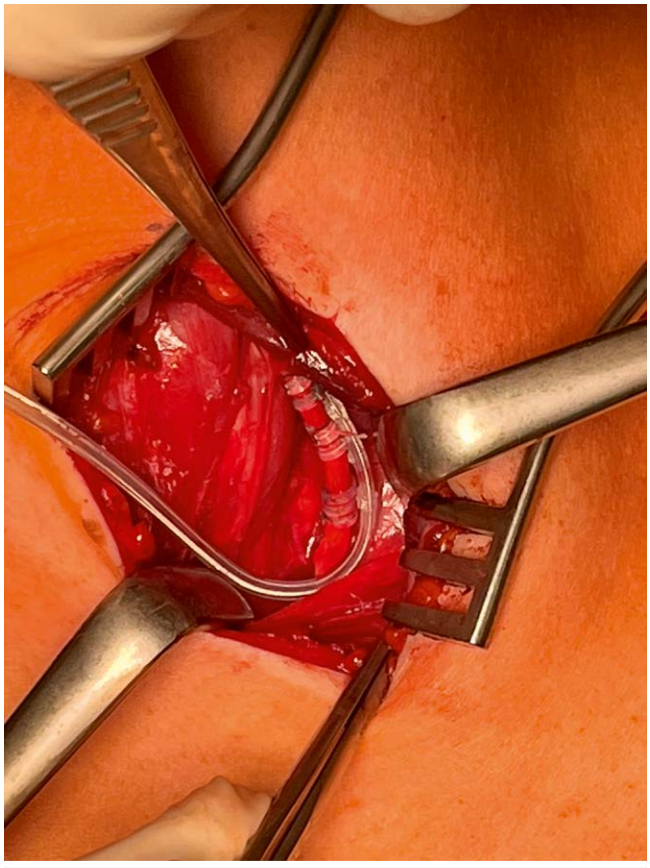



1 = Prominentia laryngis/median line
2 = Anterior edge of the sternocleidomastoid muscle
3 = Clavicula
4 = Skin incision (electrode)
5 = Skin incision (IPG)

▶ **Fig. 7** Skin incisions. Private picture (H. Möbius, 2021).




▶ **Fig. 8** Alignment of the electrodes around the vagus nerve (courtesy of LivaNova PLC Company, 2021).

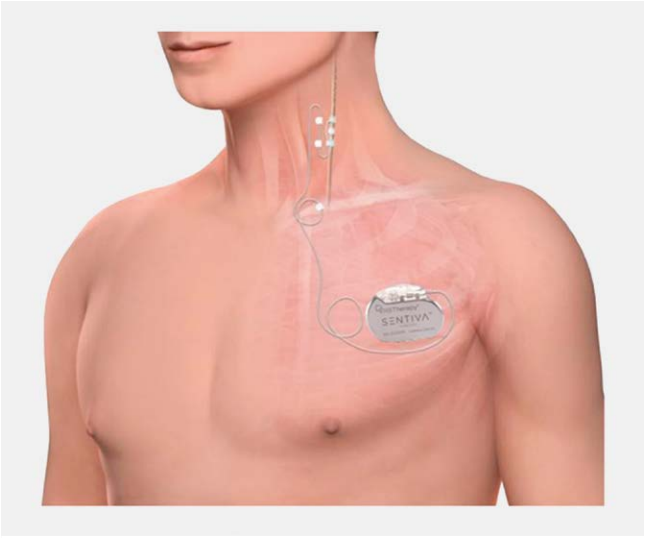


▶ **Fig. 9** Vagus nerve with stimulation electrode (private picture, H. Möbius, 2021).

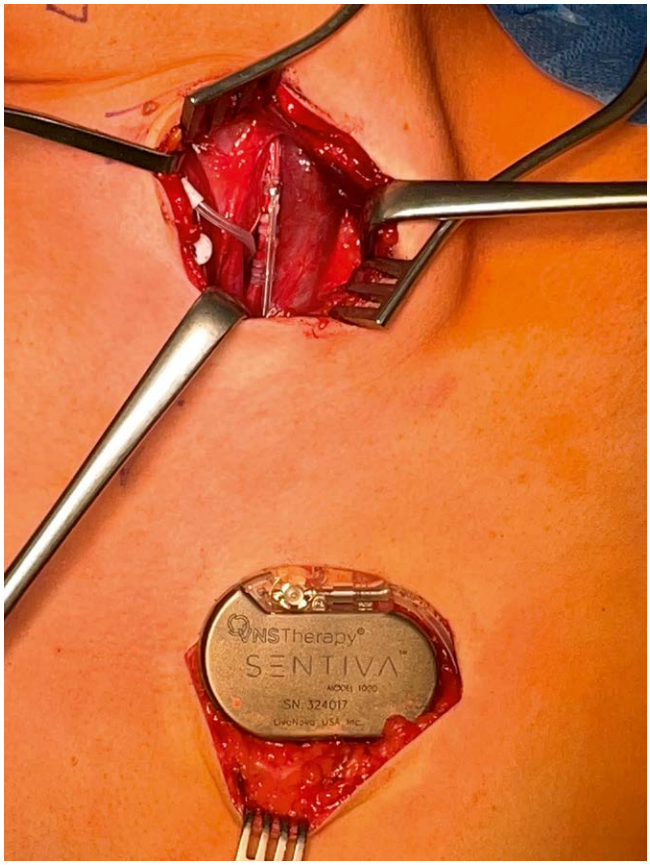
of treatment. Data about side effects of vagus nerve stimulation from 5 clinical trials that were already published in 1999, described hoarseness (28 %), paresthesia in the neck-chin area (12 %), and cough (7.8 %) one year after therapy as the most frequent therapy-associated complaints. After three years of stimulation, the incidence of hoarseness amounted to 2 %, cough to 1.6 %, and shortness of breath to 3.2 % while 72.1 % of the patients still continued VNS after three years. These side effects could be confirmed by Ben-Menachem in another trial of 2001 [96]: low-grade voice changes after three months of implantation in 62 % of the patients and 5 years after implantation in 18.7 % of the patients [100].

The results of more recent studies confirm that VNS Therapy is well tolerated and associated only with mild (physiological), transitory side effects like hoarseness or cough [101–104].

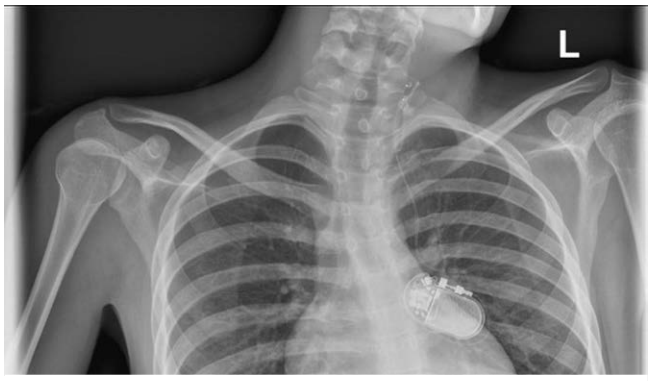
These side effects can be explained by the stimulation itself and decrease with the further course of therapy [105]; they should all be tolerable. With about one mild side effect that can be expected per person and a risk-benefit assessment, therapy should always be attempted in cases of uncontrollable epileptic seizures or depression that is refractory to conservative therapy [5].



▶ **Fig. 10** Schematic illustration of the VNS Therapy System in situ (courtesy of LivaNova PLC Company, Munich, Germany, 2021).




▶ **Fig. 11** Implants in situ (private picture, H. Möbius, 2021).




▶ **Fig. 12** Postoperative radiography (private picture, H. Möbius, 2021).

The occurrence or deterioration of obstructive sleep apnea syndrome (OSAS) under iVNS in adults and children is well-known [106, 107]. Beside increased daytime symptoms of OSAS, the disturbed sleep architecture may lead to deteriorated seizure situations [108]. Existing or newly occurring OSAS under VNS Therapy should be accompanied by closely cooperating colleagues with sleep medical control in an interdisciplinary setting; modifications of the VNS stimulation parameters of frequency and stimulation interval mostly improve the complaints [109–111]. This clinical requirement led to the fact that the youngest generation of VNS Therapy generators (model Sentiva) disposes of a so-called day/night mode allowing the programming of different stimulation parameters during two defined time frames (e. g. day/night). It would also be possible to switch off the vagus nerve stimulator by fixing the magnet on the aggregate during sleep. However, reliable data on the VNS effectiveness or the epilepsy course are currently not available [32].

Stimulation-related side effects of VNS can be well controlled by modifying the stimulation parameters. Overall, the invasive vagus nerve stimulation can be considered as safe and well-tolerated therapeutic option [112].

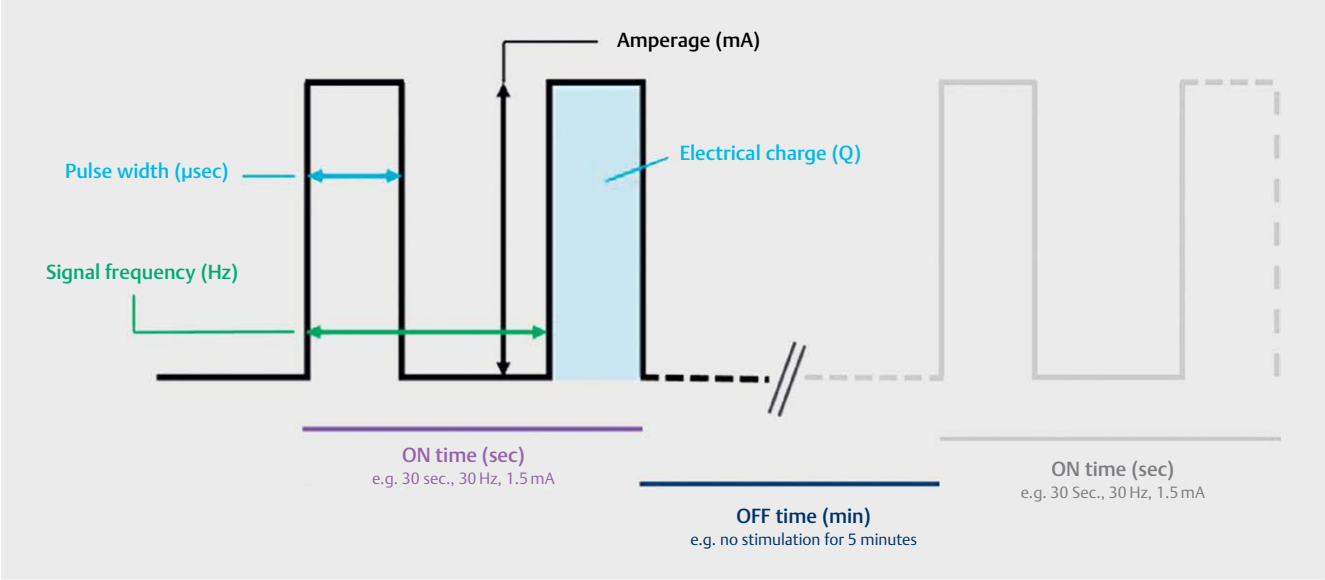
### 5.1.4. Stimulation parameters

In the context of VNS Therapy, the vagus nerve is electrically stimulated. The following stimulation parameters are relevant (see ▶ **Fig. 13**).

**(a) Amperage.** The unit for this parameter is milliampere (mA); it defines the strength of one single electrical impulse that is applied. VNS Therapy works with the constant-current principle: taking into consideration the existing resistance (R), the generator varies only the voltage (V) and controls and ensures a safe and precise stimulation of the vagus nerve. The therapeutic range amounts to 1.5–2.25 mA [113].

**(b) Pulse width.** It defines the duration of the single stimulation impulse and is programmed in microseconds (µsec). Possible programmable pulse widths for VNS Therapy are 130, 250, 500, 750, or 1,000 µsec. The result of the multiplication of the pulse width (sec) with the amperage (A) represents the electrical charge (Coulomb; Q = A * sec).

**(c) Frequency.** During a stimulation cycle (e. g. 30 seconds), the number of stimulation impulses per second defines the stimulation frequency in Hertz (Hz). Usually, frequencies of 20, 25, or 30 Hertz are applied.



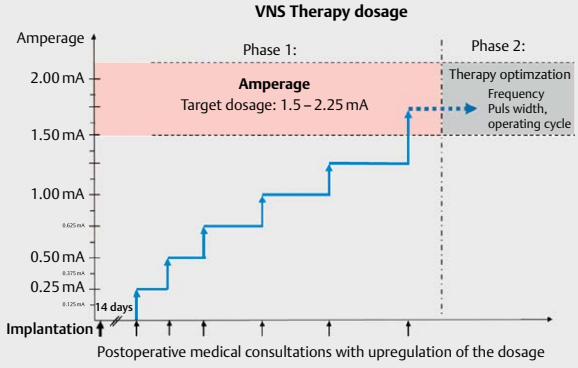

▶ **Fig. 13** Schematic description of VNS Therapy stimulation parameters (courtesy of LivaNova PLC company, 2021).

**(d) Operating cycle (ON/OFF time).** This parameter reflects the relation between stimulation (ON) and interruption (OFF) during therapy. In the practical application, each ON time is followed by a defined OFF time. The relation of both parameters may be given as percentage and is individually programmed by the user. For example, an ON time of 30 seconds followed by an OFF time of 5 minutes (300 seconds) corresponds to an operating cycle of about 10 %. In contrast to this, there are "rapid" stimulation-interruption changes like 7 seconds ON and 18 seconds OFF, which results in an calculated operating cycle of 44 % (in the literature [5] it is often described as "rapid cycle").

**(e) Duration of stimulation.** This parameter is defined as the cumulative time of VNS Therapy [114]. If a patient regularly undergoes therapy for one year, it corresponds to a therapy duration of 12 months. However, this statement has to be assessed critically because it does not reflect the actually applied electrical charge (Q) since therapy could have been interrupted during these 12 months or the amperage could have been modified.

A decisive factor for the effectiveness of VNS Therapy is a sufficient activation of the vagus nerve. The measure of vagus activation depends on the interaction of the stimulation parameters of amperage, frequency, and pulse width and follows a conventional dose-effect relationship. So, the application of shorter pulse widths may require an increased stimulation current in order to achieve the same clinical response [115, 116]. Other trials on the dose-effect relationship in animal models present similar results in dogs [117], but not in rodents [118]. Helmers and colleagues [115] explain the variable findings by the differences in the anatomy of the vagus nerve or differences in the measurement techniques.

Another important aspect for the choice of the stimulation parameters, in particular of the amperage and the impulse width, is the patients' age. All three parameters show an interdependence. Line velocity and excitation threshold of the vagus nerve are age-dependent, and the excitation threshold correlates with the applied pulse width. Koo et al. could show that the line velocity in children younger than 12 years is significantly slower compared to older patients. The authors explain this observation by the missing maturation of the vagus nerve. The excitation threshold is not only age-dependent (it is lower with increasing age) but correlates with decreasing pulse width (lower pulse widths need a higher stimulation current) [119].




▶ **Fig. 14** Schematic description of the dose-increase in VNS Therapy. Drawing: H. Möbius according to LivaNova dosage guidelines, 2021.

In 2004, Evans et al. [120] could show during surgery that the stimulation of the vagus nerve creates a compound action potential while the activation of the A fibers dominated. C fibers need stimulation current which is 10- to 100-fold higher [121–123]. As soon as the stimulation current was high enough to activate all embedded nerve fibers, the registered signal achieved its maximum. Further increase of the stimulation current (supramaximal stimu-

lation) did not increase the measured compound action potential. In this study published by Evans, the saturation was already achieved with an original current of 1 mA and a pulse width of 130 µsec. It may be assumed that scarring occurs postoperatively (fibrosis) which increased the electrical transition resistance at the nerve so that higher amperage is needed in order to achieve a maximum activation of the vagus nerve [124].

Postoperatively, the physician adjusts the IPG externally by means of a computer (tablet) and a wireless connected programming unit (wand) that is held against the chest. With therapy onset two weeks after surgery a stimulation intensity of 0.25 mA is set which is upregulated individually in 0.25 mA steps until a target dose of 1.25–2.5 mA is achieved (dose increase, phase 1, see ▶ **Fig. 14**). Frequently applied stimulation parameters are a frequency of 20–30 Hz, a pulse width of 250–500 µsec, and an operating cycle of 10–50 %.

VNS Therapy allows a multitude of operating cycles. There is for example the possibility to program a rapid cycle, which has an ON time of 7 seconds and an OFF time of 18 seconds [125]. Several trials regarding the different operating cycles (standard vs. rapid cycling) showed that the rapid cycles were superior to the standard cycles [126–128].

An animal experimental study revealed that rapid cycling has a higher impact on the electrophysiology of the hippocampus [129].

Already in 2004, Suresh and colleagues found similar results in patients with pharmaco-resistant epilepsy. They could show in their trial that the standard operating cycle (10 %) of vagus nerve stimulation as well as the rapid cycle (44 %) could reduce the frequency of seizures. However, an operating cycle of 44 % was significantly more effective in children but not in adults. Pediatric patients suffering from Lennox-Gastaut syndrome showed the highest response [130]. Another trial could not reveal a statistically significant difference in the impact of the operating cycle on the incidence of seizures [131].

Mu et al. investigated the effect of different pulse widths (130, 250, and 500 µsec) on specific brain regions in patients with major depression by means of functional magnet resonance imaging (fMRI). They could show that different pulse widths have different acute effects for the activation but also deactivation of specific brain regions [132].

In the context of vagus nerve stimulation, the objective of titration is the optimization of the current on a therapeutic level which is well tolerated by the patient. Supratherapeutic dosage should be avoided because it leads to rapid battery discharge resulting in early surgical intervention for stimulator replacement.

In order to optimize personalized therapy, the current IPG generation model 1000 (SenTiva) disposes of additional time-based functions like day-night programming (for setting two different stimulation parameters within a 24-hour interval) as well as the possibility of planned programming where dose adjustments are preset in the context of therapy settings. Narrow follow-up appointments may be reduced in this way. Day-night programming, however, does not switch between summer and winter time or other time zones. If this feature is used, the physician has to program time shifts in the generator [34].

Each patient or relative has the possibility to trigger an additional stimulation by means of a magnet in order to interrupt or reduce the severity of a seizure [133]. The triggered stimulation is generally increased in amperage by 0.25 mA and in duration by 60 seconds compared to the interval stimulation.

In studies analyzing the use of the magnet, 50 % of the patients stated that they benefit from additional stimulation in cases of seizures [134].

In general, patients with implanted VNS Therapy system (regardless of the model) always have the possibility to interrupt stimulation in cases of undesired side effects by permanently fixing (sport tape) the VNS Therapy magnet on the generator and to consult their treating physician.

5.1.4.1. Biomarker: ictal tachycardia The disturbed electrical stimulation patterns in the brain associated with epileptic seizures lead to hypersynchronous excitations in the autonomous nervous system (amygdala and hypothalamus) and consecutively to an increased heart rate called ictal tachycardia [135]. It is nowadays considered as potential biomarker and extracerebral indicator for the occurrence of a seizure in patients suffering from epilepsy.

The prevalence of ictal tachycardia in epilepsy patients amounts to 82 % [136]; in cases of temporal flap epilepsy, it develops mostly early and prior to measurable epileptic potentials in the EEG [137, 138].

In the current generation of VNS Therapy generators, ictal tachycardia became a parameter to detect seizures, which could be confirmed in several studies [139, 140].

The VNS models of Sentiva and AspireSR dispose of so-called closed-loop Cardiac-Based-Seizure-Detection (CBSD). The algorithm behind CBSD continuously measures the patient's heart rate. Over a rolling interval of 5 minutes, the average heart rate is calculated and defined as baseline. When a specific increase of the heart rate is registered with the onset of an epileptic seizure (the algorithm is able to interpret the increase dynamism), the generator is activated and starts the predefined and programmed stimulation parameters (AutoStim/autostimulation). A crucial parameter in this context is the preset level of the threshold for triggering the AutoStim. Only after exceeding this value, stimulation is started. This value may be programmed between 20 and 70 % of the relative heart rate increase.

With a set threshold of 20 %, the heart rate must increase by only 20 % in order to trigger the automatic stimulation. This setting is very sensitive, and the seizure detection algorithm can register most seizures (sensitivity of 98 %). The clinically significant effect is that vagus nerve stimulation (AutoStim) starts as closely as possible to the development of the epileptic seizure. In the clinical pivotal trials, the latency until the onset of AutoStim (with a threshold of 20 %) amounted to only about 5 seconds. This means that VNS Therapy starts less than 5 seconds after the cerebral seizure development [141].

The preset threshold is not rigid and unchangeable but adjusts to the respective situation (so-called floating threshold). When the algorithm calculates a permanently higher **baseline heart rate** (e. g., during **sports**) taking into consideration the steepness of the tachycardia over the past 5 minutes, the programmed threshold is adjusted to this new active situation (higher baseline) and accordingly increased. Thus, permanent stimulation during physical activities is avoided. Furthermore, the overall duration of the stimulation is limited by a specific feature of the generator, a technical refractory period as safety time window.

The clinical pivotal trials (E36 & E37) showed significantly that the shorter the latency of stimulation, i. e., the earlier the stimulation starts with regard to ictal tachycardia, the shorter the duration of the patients´ seizure was [140]. Other trials confirmed that the closed-loop VNS (responsive VNG Therapy) significantly reduced the seizure duration [142]. The duration of the seizures is shorter because the expansion of the pathological potentials during an epileptic seizure over the entire brain is suppressed [143]. This induces less generalized tonic-clonic seizures. With reduced generalization, also the autonomous dysfunction normalizes and shortens the duration of ictal tachycardia. Beside seizure-related risks, this normalization may also be discussed as a reduced cardiac risk. The duration of the ictal tachycardia is shorter which leads to a reduced risk of **SUDEP**. The sudden unexpected death in epilepsy patients (SUDEP) is a very rare but lethal complication of epilepsies, most probably caused by an inhibition of the cardiopulmonary function after a generalized tonic-clonic seizure [144, 145].

With the development of the Cardiac-Based-Seizure-Detection (CBSD) algorithm, the traditional vagus nerve stimulation is upgraded to a responsive system that is able to react within a very short timeframe to the onset of epileptic seizures.

The increase of the overall duration of the stimulation is limited due to the properties of the IPG. After a closed-loop (responsive) stimulation usually set to 60 seconds, an automatic refractory phase of the same duration follows. Furthermore, the normal OFF period (standard value of 5 minutes) is reset after the closed-loop stimulation so that the next regular interval stimulation occurs only after this period [32].

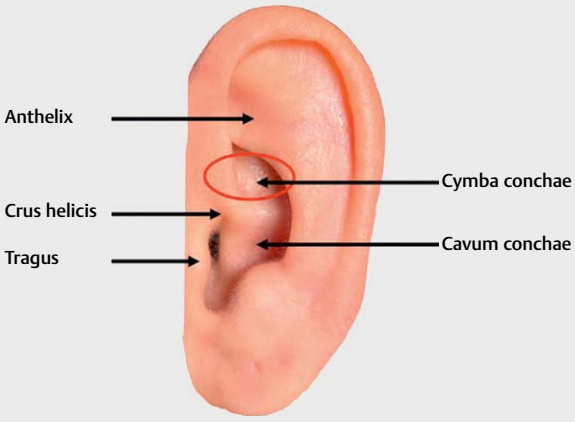
## 5.2. Non-invasive transcutaneous vagus nerve stimulation (tVNS)

Non-invasive transcutaneous stimulations are classified into auricular (taVNS) and cervical (tcVNS) procedures. The basic idea of tVNS was to perform vagus nerve stimulation via an atraumatic application pathway without the risks of iVNS (see chapter 5.1.3). Furthermore, it was intended to be less cost-intensive and simple to handle. A high therapy adherence was expected. Both methods are explicitly patient-controlled stimulations but without closed-loop function.

### 5.2.1. Transcutaneous auricular vagus nerve stimulation (taVNS)

The stimulation of the sensitive auricular branch of the vagus nerve was the first type of tVNS and is often used as synonym for transcutaneous vagus nerve stimulation (tVNS). Up to now, a multitude of publications and pilot studies are available on transcutaneous vagus nerve stimulation with most different indications. A procedure for electrical stimulation in form of transcutaneous electrical nerve stimulation (TENS) in the area of the auricular branch of the vagus nerve (ABVN) was first described in 2000 [146].

The initial investigations in the pivotal trial (CE certification in 2010 for therapy of epilepsy and depression) are based on the Nemos system (Cerbomed Company, Erlangen, Germany) [147]. The electrical stimulation is performed in the area of the cymba conchae, an area of the Ramsay Hunt zone via specifically shaped superficial electrodes. Comprehensive analyses document the ramifications of the nerve in the area of the auricle [75, 148].




▶ **Fig. 15** Model of the auricle. Red: cymba conchae = stimulation site of taVNS (private picture; H. Möbius, 2021).

▶ **Table 2** Innervation of the auricle by the auricular branch of the vagus nerve; according to Peuker and Filler, 2002 [149].

| Auricular region | Innervation by the auricular branch of the vagus nerve in % |
|---|---|
| Crus of helix | 20 |
| Antehelix | 73 |
| Tragus | 45 |
| Cymba conchae | 100 |
| Cavum conchae | 45 |

The density of the afferent sensitive fibers of the auricular branch of the vagus nerve of the auricular concha is depicted in ▶ **Fig. 15** and ▶ **Table 2**.

Accordingly, a bipolar stimulation electrode has been developed for non-invasive stimulation in the area of the external ear/the left auricle. With an external generator of the size of a mobile phone the patients select a perceivable but not uncomfortable amperage within defined limits resulting in biphasic impulses (25 Volt, 10 Hz, 0.3 ms of pulse). The stimulus intensity mostly amounts to 0.8 mA [5, 150]. Stimulation parameters like impulse frequency or stimulation intervals are set according to the indication. It is recommended to undergo therapy 4 times per day for one hour each.

The effectiveness of taVNS for therapy was initially investigated by means of a randomized, double-blind, controlled trial. The high-level group (stimulation frequency of 25 Hz) showed a significant reduction of the seizure incidence of 23.4 % compared to the low-level group (1 Hz, increasing number of seizures of 2.9 %). Higher numbers of patients were necessary to confirm the effectiveness with higher statistical power [151].

Another trial shows a reduction of the seizures in 38 % of the participants after 6 months of therapy; in 16 % even elimination of the seizures was achieved. The success rates increased with therapy duration [152].

Electrophysiological and imaging studies with healthy participants confirmed that comparable neuronal activity changes occur in taVNS like in iVNS, e. g., activity changes of innervation areas of the vagus nerve [153] or in the thalamus and the limbic system [154, 155] which were visible in the EEG.

The approval for pain therapy (pain and migraine) was achieved in 2012 [156] and for therapy of anxiety disorders in 2019 [157].

Severe side effects have not been reported up to now [158–160], especially no cardiac arrhythmia [161]. In single cases, the known spectrum of side effects comprises hoarseness, obstipation [162], nasopharyngitis, vertigo, balance disorders, nausea, fatigue, diarrhea [163], skin irritations, headaches [164, 165].

Based on the knowledge of iVNS (regarding possible cardiac side effects), taVNS has been developed for the left ear. However, recent studies in healthy participants do not show cardiac side effects even in the context of right-sided auricular stimulation [166]. A trial with patients suffering from chronic heart defects did not reveal any unfavorable effects during right-sided or bilateral stimulation [167, 168].

Currently, the system can only be purchased commercially in Germany as low-frequent electrostimulation device for symptom alleviation of sympathovagal imbalance and migraine. The patent is distributed by a medical products company from Erlangen, Germany (tVNS technologies GmbH). The treatment is not registered in the catalogue of the statutory health insurances in Germany. Currently, there is a commenting procedure of the Gemeinsame Bundesausschuss der Krankenkassen und Ärzte (GBA) (Federal Joint Committee of Insurance Companies and Physicians): Transcutaneous vagus nerve stimulation for treatment of patients with pharmaco-resistant epilepsy who are not suitable for surgical intervention or refuse it (§ 137e, SGB V [volume 5 of social insurance code]). The procedure was opened in 2017 [169].

In Germany, the system is currently used exclusively in the context of evidence finding in studies.

However, one aspect has to be questioned critically. According to the product catalogue and the website, the current provider recommends the treatment for anxiety disorders, asthma, atrial fibrillation, autism, cognitive impairment, Crohn's disease, depression, epilepsy, fibromyalgia, inflammation, migraine, Parkinson's disease, Prader-Willi's syndrome, sleep disorders, stroke, tinnitus without providing sufficient clinical evidence. It is mandatory to conduct systematic trials in order to identify the effect mechanisms and optimal stimulation modalities. Future systematic studies with standards of electrode and stimulation parameters and comparable protocols are required [170].

### 5.2.2. Transcutaneous cervical vagus nerve stimulation (tcVNS)

In the context of transcutaneous cervical vagus nerve stimulation (tcVNS) impulses are applied over the area of the cervical nervous course along the sternocleidomastoid muscle, in accordance with the historically known therapy approach of Cornings (see also chapter 2). The system of gammaCore-Sapphire™ (ElectroCore LLC, Morris Plains, NJ, USA) creates an electrical low-voltage stimulation with five 5,000 Hz pulses and a frequency of repetition of 25 Hz. The maximally possible output current is 60 mA. Acute (with pain onset) or prophylactic (several times per day) applications with durations of seconds to minutes are recommended (Instructions of Use, GammaCore Sapphire™, ElectroCore LLC, Morris Plains, NJ, USA) [171].

Initially, the procedure was investigated for the treatment of chronic headaches. During application, a discomfortable twitching and local pains in the neck region are observed as side effects. This stimulation procedure is not CE approved and can only be purchased commercially. tcVNS is FDA approved for the treatment of migraine and cluster headaches [172, 173] and is recommended by the manufacturer for the treatment of primary headaches (cluster headaches, migraine, and hemicrania continua) and drug-induced headaches in adults.

The manufacturer mentions the following contraindications regarding the application of tcVNS: pre-existing active implanted medical products like pacemakers, hearing implants, or other implanted electronical devices, carotid atherosclerosis, condition after cervical vagotomy.

Possible risks and complications are: temporary larynx irritation, dysphagia, dyspnea, cough, hoarseness or changed voice, muscle tics, discomfort or pains during stimulation, dysgeusia under treatment as well as paresthesia or dysesthesia that may last even after the treatment period. Furthermore, skin irritation is mentioned in the product catalogue as an allergic reaction to the electrode gel as well as increasing headache symptoms, syncopes, numbness, or vertigo (Instruction of Use, GammaCore Sapphire™, ElectroCore LLC, Morris Plains, NJ, USA).

Currently, transcutaneous electrical stimulation of the vagus nerve is the object of research in the disciplines of psychology, immunology, cardiology as well as pain or plasticity research with desired potential for future medical application [174, 175].

It is mandatory to conduct systematic trials in order to identify the effect mechanism and optimal stimulation modalities. Due to the multitude of studies published on the topic of transcutaneous cervical vagus nerve stimulation with sometimes confusing and incomparable designs, the "Minimum Reporting Standards for Research on Transcutaneous Vagus Nerve Stimulation (version of 2020)" were formulated at the beginning of 2021 in order to guarantee clear standards for future studies in the sense of a guideline [174].

### 5.2.3. Percutaneous auricular VNS (paVNS)

This rather young type of VNS is minimally invasive and already a research topic. With 2–3 small needle electrodes the skin in the target area of the cymba conchae is penetrated [176]. Possible side effects are skin irritations (dermatitis), local bleeding, stimulation pain, vertigo. Sufficient evidence-based data are currently not available [175]. Currently, no assessment on the validity and on the therapeutic effect can be given.

Considering the currently available results (see also chapter 7) of invasive and transcutaneous vagus nerve stimulation, there is only sufficient evidence for iVNS. In Germany, the transcutaneous procedures are currently distributed only commercially (taVNS) or are not CE approved (tcVNS, FDA approved).

## 6. Patient selection/predictors for VNS response

According to the current criteria of the International League Against Epilepsy (ILAE) and the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF; German Association of the Scientific Medical Professional Societies), invasive VNS Therapy is one option for treatment of patients with pharmaco-resistant epilepsies, i. e. patients who do not satisfactorily respond to drugs alone. These criteria are characterized by two failed therapy attempts with antiepileptic drugs despite adequate dosage and duration in mono- and/or combination therapy or missing other therapeutic options or in patients who are not suitable for epilepsy surgery or refuse it.

In about one third of the epilepsy patients, sufficient control of the seizures cannot be achieved by means of anticonvulsive drugs [32].

In Europe and many other parts of the world, VNS Therapy may be applied age-independently.

In this heterogenous patient population, vagus nerve stimulation has a mainly palliative effect, it does not lead to healing from epilepsy. Only in about 10 %, complete elimination of the seizures may be achieved [177, 178].

According to the current AWMF guidelines, VNS Therapy may be applied age-independently in the context of depression therapy in patients with chronic or recurrent depression who do not respond to drug therapy or who suffer from treatment-resistant major depression.

Valid predictors for a positive response to invasive VNS are currently not available, however, some publications with mostly small numbers of cases discuss individual predictors [179–183]. Possibly favorable factors are the absence of bilateral interictal activity, the presence of malformation of the cortical development, early implantation [184, 185] as well as reduced synchronization in the surface EEG [186, 187].

A clear contraindication for iVNS is a condition after left-sided vagotomy.

The multivariate analysis revealed that a higher age at epilepsy onset (> 12 years) and predominantly generalized seizure types were predictors for achieving seizure-freedom [197].

## 7. Therapy results and quality of life

The main objective of the initial trials was the evidence that epilepsies which are refractory under conservative therapy respond to this new therapy option of stimulation procedures. The main focus was placed on the responder rate of patients who achieved a reduction of seizures of 50 % or more. The complete elimination of seizures was observed in about 10 % of the patients, among them even patients with severe complex epilepsy types. Already 50 % of reduced seizures significantly increased the quality of life of the affected patients. The possibility of autonomous magnet utilization strengthened the patients' sovereignty [5].

Compared to interventions in the context of resective epilepsy surgery, stimulation therapy with invasive vagus nerve stimulation has the major advantage of reversibility [34]. Negative effects on cognition as they have been observed with antiepileptic medication have not been reported [5].

### 7.1. Vagus nerve stimulation for epilepsy refractory conservative therapy

#### iVNS

Vagus nerve stimulation is applied to reduce the incidence of epileptic seizures. In class-I trials, an average seizure reduction of 25–28 % was found compared to a placebo rate of 6–15 %. Open trials report about clearly higher effects [188]. By definition, a patient is considered as responder to vagus nerve stimulation therapy with a reduction of at least 50 % of the seizure incidence. In the conclusion of the studies, an additional reduction of the severity of the seizures is regularly reported. This includes the following aspects: shorter duration of the seizures, reduction of postictal complaints, longer seizure-free periods or absent development of generalized seizures due to VNS therapy with only focal seizure pattern.

In 1995, the VNS study group published a randomized controlled trial on invasive vagus nerve stimulation in 114 patients. The group with therapeutic stimulation showed a significant reduction ($p = 0.02$) of the seizure incidence compared to the initial baseline and compared to the group with the non-therapeutic stimulation approach. 31 % of the patients with therapeutic stimulation had reduction of over 50 % of the seizure incidence [189]. In 1998, Handforth et al. also showed a significant reduction of the seizure incidence of 28 % in the therapeutically stimulated group ($p = 0.04$) of 198 patients with complex-focal seizures [190]. The level of improved seizure control by VNS was considered as comparable to the application of an additional medication [191].

A prospective randomized controlled trial on VNS Therapy in children with a similar design as the blinded pilot study in adults did not show significant differences with regard to the responder rate and severity of seizures between the therapeutically and subtherapeutically stimulated groups [192]. After a follow-up period of 19 weeks, 26 % of the patients were considered as responders. Even improvements regarding the severity of seizures were observed ($p < 0.001$). It is notable that a relevant percentage of patients of the subtherapeutically stimulated control group belonged to the responders. A possible therapeutic effect even of low stimulation doses is discussed [32].

In 1999, Morris and colleagues published first long-term data of VNS Therapy in 440 patients. One of the most important discoveries was the observation of a long-term effect which means that the effectiveness of the treatment increased with longer application periods. After one year of VNS Therapy, 36.8 % of the patients achieved a reduction of seizures of 50 %, after 2 and 3 years, there were 43.2 and 42.4 %, respectively [32, 193].

In addition to the reduction of the seizure incidence, Tatum et al. showed the effect of VNS on the duration of the seizures and the postictal complaints in 71 % of the patients as well as a reduction of the number of applied anticonvulsive drugs [194]. McHugh et al. also described a reduction of the severity of the seizures and postictal complaints [195].

In 2014, Orosz and colleagues revealed in an assessment of the long-term effect of VNS Therapy with a follow-up period of 2 years in 347 children that 43.8 % of the patients had a ≥ 50 % reduction of the seizure incidence. Furthermore, the duration and severity of the seizures improved as well as postictal complaints, quality of life, and clinical overall impression. In addition, Orosz and colleagues describe a significant dose-effect relationship in responders [196].

In 2015, Englot et al. [197] published their results on the effectiveness of VNS with a particular focus on seizure-free rates and their predictors. Data of 5,554 patients from a registry were analyzed and a literature review of 78 studies with 2,869 patients was conducted. Responder rates and the percentage of completely seizure-free patients increased with longer duration of stimulation. After 24–48 months, 63 % of the patients belonged to the group of responders and 8.2 % of the patients were considered as seizure-free. The multivariate analysis revealed that a higher age at epilepsy onset ( > 12 years) and predominantly generalized seizure types were predictors for achieving seizure-freedom. Also in the context of literature research, 60.1 % of the patients belonged to the responders, 8.0 % were seizure-free [32].

In 2007, Montavont et al. could show comparable responder rates in 50 patients [198] and in 2006 Alexopoulos et al. in 46 children [199] with a follow-up period of 3 and 2 years, respectively. In a prospective trial, Ardesch et al. [200] reported the reduction of the average seizure incidence of up to 50 % after six years. 47 % of the examined patients reported a reduction of the severity of the seizures and the postictal period.

An evaluation of 51 patients by Hamilton et al. (2018) could show a positive outcome in 70 % of the patients due to the heart rate-based recognition of seizures and the closed-loop autostimulation [201]. Results of Data et al. in 2020 confirm the seizure reduction with autostimulation in 28 % of their patients [202].

A recent meta-analysis published by Debue et al. in 2020 shows also in the severe epilepsy type of Lennox-Gastaut syndrome a responder rate of 54 % with the safe and well-tolerated VNS Therapy [203].

The chapters 5.1.4.1 and 7.3 describe comprehensively the problems of ictal tachycardia as well as the T wave alternans; a reduced cardiac morbidity and mortality (SUDEP) [204] achievable with iVNS therapy increases the quality of life and the life expectancy. Thus, the benefit of VNS Therapy is superior to the described cardiac risks [205]. The persistence of epileptic seizures leads to an increased morbidity and mortality.

The status epilepticus is a life-threatening emergency; between 24 and 38 % of the cases have a lethal outcome. Their incidence increases with age-associated cardio-respiratory concomitant diseases [206, 207]. Due to iVNS therapy, the risk for a status epilepticus can be reduced by factor 3; furthermore, a reduction of factor 2 for seizure-associated hospitalization is observed [208].

Even in cases of refractory or super-refractory status epilepticus, acute VNS implantation may interrupt this life-threatening condition in 74 % of the cases [209].

Beside influencing the seizure situation, one side effect of vagus nerve stimulation is the positive effect on the quality of life, vigilance, and cognition (see also chapter 7.3). In a prospective randomized parallel-group, open-label designed trial, Ryvlin et al. [210] investigated the effects of VNS on the quality of life. The quality of life of the patients who additionally underwent VNS improved significantly compared to a control group where only the pharmacotherapy was optimized. There was a clear superiority of the VNS group [32, 211].

VNS also has a positive effect on the mood, memory, and quality of life of the patients [212] assessed by means of visual analogue scales (VAS) without iVNS causing cognitive or systemic side effects like fatigue, psychomotor slowing, irritations, or nervousness in contrast to most anticonvulsive drugs [213]. Cerebral nerve complications [214] or teratogenicity [215] as well as changes of the cardiac rhythm, pulmonary function, or gastrointestinal motility and secretion have not been described [5]. Studies confirm an improved cognitive function under invasive vagus nerve stimulation [216] as well as reduction of anxiety under iVNS therapy. The reduction correlates with the reduction of the seizure incidence and might be considered as possible secondary psychological advantage of the treatment [5, 217].

The patients' satisfaction with iVNS is generally observed. Studies confirm that 97, 85, and 72 % of the users after one, two, and three years, respectively, continue the iVNS therapy in cases of satisfaction. About 75 % of the patients opted for a generator change after battery discharge [218]. Due to the autonomously triggered stimulation with the magnet in cases of seizures, the patients have the feeling of better controlling their seizures which compensates the described phenomenon of learned helplessness of epilepsy patients [219].

Further also patients under guardianship with a lower intelligence quotient showed a better quality of life with improved attention, speaking ability, balance as well as performance of everyday tasks [220].

Another trial [5] showed significantly happier moods in 20 % of the questioned iVNS patients under stimulation than before therapy; 5.71 % were tenser. 8.57 % of the patients complained postoperatively about a deteriorated sleep quality; 2.86 % reported about improved sleep. 17.24 % of the iVNS patients mentioned improved concentration under stimulation therapy. However, it must be considered that sometimes patients took antidepressants simultaneously because of comorbid depression. 60 % of the iVNS users would opt again for iVNS and only 11.43 % felt impaired by the device in their daily routine [221].

Carius et al. [222] report about an improved psychological mood in 24.19 % of the patients. Some of them who did not experience reduction of the seizures despite iVNS did not wish explantation of the IPG due to the subjectively perceived positive effect on their mood [5]. Further trials confirm the improved mood after therapy durations of sometimes even only three months [223, 224] independently from the improved seizure control/responder rate or specific setting parameters.

Based on the standardized tests of POMS and QOLIE-89, Klinkenberg et al. [225]investigated prospectively the effect of invasive vagus nerve stimulation on the mood and the quality of life in relation to the seizure control. After six months of therapy, mood and quality of life as well as cognition showed significant improvements. Also Sherrmann et al. confirmed in their study that 56 % of the patients experienced a subjectively perceived improvement of the quality of life [226].

In a double-blind randomized trial, Dodrill et al. [227]showed less emotional and psychological problems in the group with high iVNS parameters compared to lower stimulation. It becomes obvious that the iVNS has a positive impact on the moods, independently from the seizure control. The quality of life of iVNS epilepsy patients cannot be measured alone with the effect on the seizure situations; other factors have to be taken into account that might contribute to an improved overall situation [5].

Bernstein et al. [228] as well as Alexopoulos et al. [229] described a statistically significant reduction of the number of visits in emergency units, hospitalizations, and duration of inpatient stays after iVNS implantation. The average hospitalization that patients underwent in the context of their epilepsy disease was significantly reduced ($p < 0.001$). iVNS reduces hospitalization.

By use of the QOLIE-89 and ELDQL, two standardized questionnaires on the quality of life of epilepsy patients, McLachlan et al. [230]analyzed in a prospective study the outcome of iVNS therapy after one year with regard to seizure incidence, antiepileptic medication, and quality of life. With a responder rate of 19 %, the number of anticonvulsive drugs could be reduced under stimulation therapy in 43 %. Significant improvements of the quality of life (significant improvement concerning attentiveness/concentration, memory as well as speech) as well as improvement of the severity of seizures were calculated without correlation with the seizure incidence. 84 % of the patients confirmed a subjectively perceived improvement of their overall situation under iVNS therapy. In contrast, Chavel et al. [231] evaluated the QOLIE-89, BAI, BDI tests and found no statistically significant difference regarding the quality of life and the comorbid depression with a responder rate of 54 %. However, significantly less anxiety symptoms were observed.

In epilepsy patients with the comorbidity of depression, the suicide rate is increased by 22 %. Evaluations of 636 patients revealed a statistically significant reduction of the mortality, suicides, and suicide attempts under iVNS therapy [232].

iVNS therapy has a positive effect on patients with conservatively therapy-refractory epilepsy by improving their quality of life as well as their overall situation, whereas not always an optimized seizure control can be achieved. Also, other parameters positively influence the quality of life under iVNS. Cordes et al. showed in only 30 % of seizure responders that 60 % of the patients would opt again for therapy. It seems to be important that patients who do not benefit from iVNS regarding their epileptic situation are asked about changes of their quality of life since therapy onset before explanting or deactivating the IPG because of a missing objective effect [5].

### tVNS

As a non-invasive therapy procedure, transcutaneous VNS allows interesting applications under certain circumstances, for example as an alternative to invasive VNS or as possible non-invasive step to predict the success of invasive VNS. In this way, patients could be identified prior to iVNS implantation who probably turn out to be responders to therapy. Future studies are needed to confirm a clear effectiveness of transcutaneous VNS [32, 233].

In 2012, the evidence of a reduction of the seizure incidence was performed initially in a proof-of-concept study of NEMOS (Cerbomed Company) transcutaneous VNS (tVNS), however, without achieving the set threshold of 50 % reduction of the seizure incidence [234].

In a randomized, double-blind controlled trial of 2016, the effectiveness of tVNS was investigated over a 20-weeks observation period. The seizure incidence decreased significantly by 34 % in patients of the 25 Hz high level group [235].

A retrospective analysis of Cordes in 2019 [5] identified one third of 12 tVNS patients as responders, 20 % became seizure-free in a follow-up period of about 5 years. In the study of Stefan et al. from 2012, a reduction of the average monthly seizure incidence was observed in a clearly shorter follow-up period of 9 months without achieving the reduction of 50 % [236]. This aspect is discussed as possible hint to the fact that VNS therapy should be planned as long-term treatment in order to increase the treatment effect [237].

Positive effects on cognition could be confirmed by Jacobs et al. in a simple blinded study with older healthy participants with an improved associative memory performance after only one stimulation session [238].

According to Morris et al., the non-invasive tVNS is associated with less side effects compared to iVNS; he discusses a higher tolerance of the less cost-intensive device that is easier to handle [239]. However, it must be taken into account that the therapy adherence of a required long-term treatment is reduced.

Overall, a tendency of reduced seizures was observed under tVNS therapy along with a slight tendency to reduction of the average number of monthly taken drugs per patient [5].

While the majority of cognitive functions and also the measurement values of the BDI were constant over the time of tVNS therapy in single studies [240], others showed a significant improvement of SAS, SDS, and Liverpool Seizure Severity Score (LSSS) [241] and improvements of the LSSS, the MADRS, and the CGI-S [242]. In these studies, also positive effects on the seizure severity, mood, anxiety disorders were observed during tVNS beside an improved seizure situation. It seems to be appropriate to assess the outcome of tVNS also regarding reduced anxiety, improved mood and concentration, and in particular the subjective perception of the patients of an improved overall situation and the quality of life, beside its effect on the seizure incidences [5]. Independently from the seizure control, tVNS has positive effects on the mood and the quality of life [5, 240, 241].

## 7.2. Vagus nerve stimulation for chronic depression

### iVNS

The results of the studies mentioned in chapter 7.1 on the quality of life show an improved mood situation as well as quality of life under invasive vagus nerve stimulation in epilepsy patients, independently from the influence on the seizure control [243] and confirm the antidepressant effect of iVNS which is of great importance for mood disorders in epilepsy patients regarding the high comorbidity. Vagus nerve stimulation is used for treatment of depression and turned out to be effective in several trials [244]. Different rating scales are used for measurement like the 24 item Hamilton Depression Rating Scale (HDRS24), Montgomery-Åsberg Depression Rating Scale (MADRS), Geriatric Depression Scale (GDS).

Based on the observed antidepressant effect of VNS in epilepsy patients, trials on the effectiveness of VNS in therapy-refractory depressions have been conducted [38]. In a 10-week sham stimulation-controlled study, there was first no statistical difference between the group of sham stimulation and the therapeutic stimulation with regard to the 24 item Hamilton Depression Rating Scale (HDRS24). In the open label extension study over one year ($n = 205$), significant improvements of the HDRS24 score became obvious [245]. In 2005, the FDA approval of VNS was achieved for treatment of therapy-refractory depression.

In the context of a prospective, non-randomized trial, Aaronson et al. investigated a total of 795 patients with drug therapy refrac-

tory depression over a 5-year period. According to the MADRS, VNS therapy showed a response rate of 67.7 % and a significantly high remission rate.

iVNS has an effect on affect and cognition [32]. Sackeim et al. [246] observed cognitive improvements in non-epileptic depressive patients under iVNS therapy.

An improved daytime vigilance under VNS is assumed due to improved reticular activating system function even if this mechanism based on invasive vagus nerve stimulation is unclear [72].

Patients with depression show a disturbed balance of the autonomous nervous system with increased sympathetic tonus resulting in physiological stress reactions with hypertonia, tachycardia etc. They have an increased risk to develop arrhythmia and sudden cardiac death [247, 248]. Depressions, acute stress, and rage may cause angina pectoris and heart attacks [249]. According to the KORA heart attack registry, depression ranks third after smoking and diabetes as risk factor for heart attack beside hypertonia [250]. Obese patients with comorbid depression even have a triple risk. With a response to VNS therapy, the cardiac morbidity and mortality are reduced.

The increased suicide rate of depressive patients described in chapter 7.1 is reduced with VNS therapy leading to a lower mortality rate, suicides, and suicide attempts [251].

### tVNS

Even for transcutaneous VNS, antidepressant effects are described. Hein et al. [252] were the first to report about antidepressant effects of transcutaneous auricular VNS in a randomized controlled pilot study. Kraus et al. [253] detected in 22 healthy participants a reduced BOLD signal (blood oxygenation level dependent signal activities) in the limbic system and temporal brain regions and increased BOLD signals in the island, the precentral gyrus on both sides as well as the right thalamus by means of functional MRI under transcutaneous VNS. Psychometric tests revealed a significant improvement of the well-being after stimulation. Further studies [254, 255] also identified clear antidepressant effects of transauricular VNS, some patients even achieved remission [32]. Positive effects on cognition have been described for transcutaneous VNS with improved associative memory performance after only one stimulation session [256].

## 7.3. Other therapeutic effects – future indications?

It has been proven that epilepsy patients have a significantly increased risk for high blood pressure, depression, stroke, gastrointestinal disorders, and trauma due to falls [257]. The evaluation of numerous trials on VNS Therapy from the past two decades showed multiple positive effects on other diseases so that possibly other therapy indications may be expected [258].

### Cardiology

Chapter 5.1.4.1 describes comprehensively the occurrence of ictal tachycardia in patients with epilepsy, the prevalence amounts to 82 %. By integrating the Cardiac-Based Seizure Detection (CBSD) in the implantable vagus nerve stimulator, not only generalized tonic-clonic seizures are reduced, but also the duration of ictal tachycardia. This means a reduced cardiac risk and thus a significant reduction of the so-called SUDEP risk (sudden unexpected death in epilepsy patients).

Epilepsy may additionally cause most severe ECG abnormalities and cardiac arrhythmia with a significantly increased risk for sudden cardiac death (SCD). One critical parameter in this context is the T wave alternans (TWA). The estimated risk for life-threatening arrhythmia due to TWA was confirmed in studies with 7,000 patients with numerous cardiac diseases [259].

Patients after myocardial infarction with stable coronary heart electricity had low TWA values after one year (21.1 µV) which indicates a favorable restoration of heart substrate and physiology [260].

The TWA limit was defined to 47 µV. Patients with TWA values beyond this limit value had a 4–7-fold higher probability to develop life-threatening arrhythmia [258].

Prior to VNS therapy, 82 % of the patients had TWA values above the 47 µV value. VNS therapy reduced the TWA value in 70 % of the patients to a level of 21 µV and thus also the seizure-associated cardiac dysfunctions [261, 262]. Libbius and colleagues describe a reduction of ventral tachycardia of over 73 %. Furthermore, this effect is dose-related and correlates strongly with the used VNS therapy power intensity [263].

In chapter 7.2 the significance of depression is already described as third most important risk factor for heart attack according to the KORA heart attack registry. A response to VNS therapy reduces the cardiac morbidity and mortality.

In 2015, the vagus nerve stimulation obtained the approval for therapy of chronic heart failure (CHF) in Europe. In a trial with 60 heart failure patients, a significant improvement of some cardiac parameters could be shown [264]. Currently, subsequent investigations and evaluations are conducted in Germany in the context of the VITARIA registry: Prospective observations of therapy of symptomatic heart failure with the vagus nerve stimulation procedure; application in the DRKS (Deutsches Register Klinischer Studien, German Registry of Clinical Trials) [265].

### Pain therapy

Headaches and facial pains rank among the frequent pain diseases. They may be treated with or without drugs. In cases of headaches and facial pains that are difficult to diagnose and to treat, multimodal pain therapy may lead to positive results [266, 267].

Already in the first years of VNS Therapy, it could be shown in 2000 that vagus nerve stimulation can effectively reduce pains in humans [268]. In their study, Busch et al. found a lower mechanical pain sensitivity with tVNS [269]. In 2012, transcutaneous vagus nerve stimulation was approved in Europe for pain therapy with application in the area of the auricle (auricular branch) [270]. Epilepsy patients with the comorbidity of migraine showed reduced migraine symptoms under tVNS therapy [271–273].

In the current AWMF guidelines (status of September 2021), VNS is mentioned in the following documents:

- Application of neuromodulating procedures for primary headaches (S1, registry number 062–008, status of 2011, currently under revision and application for re-submission on August 31, 2021)
- Therapy of migraine attacks and prophylaxis of migraine (S1, registry number 030–057; status of August 31, 2018): The effectiveness of non-drug procedures has not been sufficiently

investigated for the therapy of acute migraine attacks. The transdermal stimulation of the vagus nerve (taVNS) has an effect on cluster headaches proven in a double-blind study [274]. In a pilot study, the method for treatment of acute migraine attacks was effective [275, 276]. Further studies are missing that confirm the effectiveness and analyze the long-term course. The stimulation device that has been used in the trials is currently not available in Germany.

- Cluster headaches and trigemino-autonomous headaches (S1, registry number 030–036, status of 2015, currently under revision): In a current migraine update, the following is postulated based on the current study situation: The stimulation of the vagus nerve (tVNS) can be successful for migraine prophylaxis. However, it cannot be considered as surely effective [277]. In single cases, it is a suitable addition to the therapy regimen [278–280].

Currently, 3 research projects are registered for therapy of pain syndromes and chronic migraine in the German Registry for Clinical Trials [281].

### Gastroenterology

Gastrointestinal diseases like irritable bowel syndrome and gastrointestinal bleedings are more frequently observed in epilepsy patients than in the healthy control group. The hazard ratio for gastrointestinal bleedings of patients with generalized epilepsy amounts to 3.50 (95 % CI, 2.59–4.72). The irritable bowel syndrome is present in 16 % of epilepsy patients compared to the healthy control group with 3 % (p = 0.04) [282, 283]. With VNS therapy and reduction of the seizures, also a reduction of these symptoms may be expected. In a small clinical trial with patients suffering from Crohn's disease, clinical and endoscopic remission was found after 6 months of iVNS therapy [284, 285].

### Rheumatoid arthritis

Different side effects of iVNS therapy may be explained by the vagal anti-inflammatory circle [284]. Epilepsy patients with comorbid rheumatoid arthritis showed a reduction of proinflammatory cytokines (TNF, IL-1β, and IL-6) under iVNS therapy and an improved rheumatoid arthritis. These results reveal that iVNS therapy has an anti-inflammatory effect via immunomodulatory approaches of the autonomous nervous system [286].

### Cognition in patients with Alzheimer's disease

Beside the already described antidepressant effect of VNS therapy for epilepsy patients [287], effects possibly also exist on the cognition of patients with Alzheimer's disease. There are hints to a positive effect of VNS therapy on the cognitive performance [288–290], however, they are controversially discussed [291].

### Tinnitus

Numerous studies investigate the therapeutic effect of VNS on tinnitus. The current AWMF guideline on chronic tinnitus (S3, registry number 017–064, status of September 15, 2021) gives the following evidence-based recommendation: Transcutaneous or invasive vagus nerve stimulation alone or in combination with acoustic stimulation is not recommended for chronic tinnitus. Transcutaneous vagus nerve stimulation as well as invasive, cervically implanted stimulation can be safely applied, however, there is no evidence for an effect on chronic tinnitus.

## 8. Health economics: cost-benefit analysis

From a health economic point of view, the assessment, analysis, and evaluation of general and disease-specific costs is also necessary for neuromodulatory therapy [292]. For cost assessment of health economic analyses, the cost-of-illness method (COI) is applied that differentiates between direct (outpatient and inpatient medical care, treatments, diagnostics, therapies, rehab, transportation, remedies and aids, drugs, nursing services), indirect (reduced working time, absences from work, early retirement, unemployment, early mortality), and intangible (sleep disorders, cognitive deficits, depression, social isolation) disease-specific costs [293].

High direct costs occur in the context of the first diagnosis of epilepsy, but also in therapy-refractory courses and status epilepticus. As chronic diseases, epilepsies cause high costs with mostly long-term course, time- and cost-intensive diagnostics and the necessity of permanent drug therapy. According to the German Federal Statistical Office (Statistisches Bundesamt), the epilepsy-related costs amounted to 17.8 billion Euro in 2016, which corresponds to 0.5 % of the annual health-related expenses. Especially in the context of the first diagnosis of epilepsy, high costs arise due to the intensive initial diagnostic measures that decrease in the following years. In Germany, about 14 % of disease-related costs exist due to newly diagnosed epilepsies [294, 297].

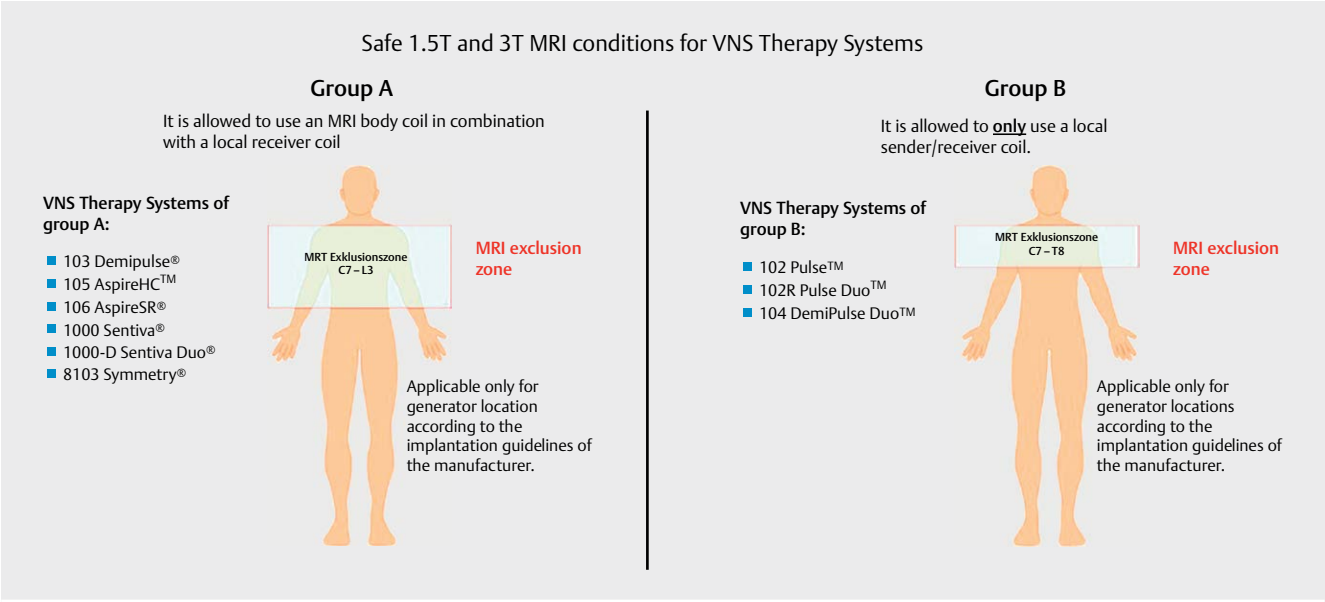
For VNS Therapy, a middle to long-term cost effectiveness could be proven. A study from the USA calculated the reduction of the annual treatment costs after VNS implantation to 2,742 Euro in comparison to only conservative therapy. Already 10 years ago (in 2010/2011) when the implantation costs were higher compared to the current reduced DRG situation, a cost effectiveness could be achieved after 11 years considering the direct epilepsy-specific costs [295]. Taking into account the indirect and intangible costs, Forbes (2008) [296] assumes an earlier rentability; his analysis confirms a cost reduction of 5,270 Euro per quality-adjusted life year.

Because of the limited data situation, no clear statement can be given regarding the cost-effectiveness of transcutaneous VNS in cases of therapy-refractory epilepsy [297].

## 9. Invasive vagus nerve stimulation from an interdisciplinary point of view – particularities

### 9.1. Magnet resonance imaging (MRI)

According to their approval, the current VNS Therapy systems are MRI compatible to a limited extent. This means that defined conditions have to be met to apply 1.5 T and 3 T MRI scanners. Particular attention must be paid to the used radiofrequency coils. As depicted in ▶ **Fig. 16**, some VNS Therapy models (group A) allow the application of a body coil as sender unit (Tx) in combination




▶ **Fig. 16** MRI guideline. Drawing by H. Möbius, 2021, according to LivaNova, MRI with the VNS Therapy System, Guidelines, August 2020. Further specifications can be retrieved from the LivaNova VNS Therapy Manual of 2020.

with a local receiver coil (Rx). Older models (group B) may only be used with a specific sender and receiver head coil (Rx/Tx) which clearly limits the possibilities of application. A precondition for both groups is a correctly implanted VNS Therapy system according to the manufacturer's manuals (in the upper left thoracic area, subclavicular and above the 4$^{th}$ rib).

In preparation of MRI, the according center reads out the generator and thus ensures that the function is regular before MRI (no cable break). During MRI scan, the VNS system should be switched off (stimulation flow set to 0 mA). In cases of possible local pains, discomfortable complaints, or flushing, the examination must immediately be interrupted. The VNS Therapy patient magnet is not MRI compatible and must not be brought into the examination room [35].

Numerous trials have been published since the approval of the VNS Therapy confirming the tolerability and safety for patients with the implanted VNS Therapy System. Two review articles comprehensively describe the knowledge of the past two decades [297, 298].

## 9.2. Other warnings

According to the safety information of the manufacturer, the safety and/or effectiveness of VNS Therapy is not proven for patients with known condition after therapeutic brain surgery or brain trauma, dysautonomia, obstructive pulmonary diseases including shortness of breath and asthma, peptic ulcer disease, vasovagal syncopes, cardiac arrhythmia as well as progressive neurological diseases or existing hoarseness. Also, other types of simultaneous brain stimulation are not admitted [35].

The presence of a **pacemaker** or **cardiac defibrillator** at the same time is no contraindication for VNS Therapy. The different aggregates, however, should have a minimum distance from each other and the electrode cables of both systems should not cross. Programming of the different aggregates should be performed at different times. The activation of the CBSD is not recommended because the technical signals of the VNS might be misinterpreted by the CBSD algorithm and possibly a false autostimulation may be triggered.

Preexisting therapy with **betablockers** should be discussed with the cardiologist in the sense of benefit-risk evaluation.

For patients with **obstructive sleep apnea syndrome (OSAS)**, descriptions are available that the OSAS symptoms might be enhanced with VNS therapy. In this patient group, a close interdisciplinary cooperation with a sleep-medical center should be ensured in cases of VNS implantation. The use of the day-night programming (model SenTiva, LivaNova Germany GmbH, Munich, Germany) should be discussed or placing the magnet on the iVNS during nighttime in order to interrupt the stimulation therapy.

For patients with implanted VNS, a possibly required **radiotherapy** may be limited (treatment with irradiation, cobalt devices, and linear accelerators) in the VNS implantation area. This therapy might damage the generator. However, the actual effect of the radiation on the IPG is not known [291].

The use of short-wave diathermia, microwave diathermia, and therapeutic ultrasound diathermia is contraindicated in patients with implanted VNS system. However, **the application of diagnostic ultrasound and radiography is not limited**. In cases of mammography, a particular position must possibly be taken [291].

The use of **monopolar coagulation** above the implantation area in the context of surgical interventions should be avoided.

VNS may be continued during **pregnancy** [299]; according to the safety instructions of the manufacturer, however, the effectiveness and safety of the device are not confirmed in pregnant women [291].

In cases of **swallowing disorders**, the genesis should be considered. Accordingly, the active stimulation may lead to a deteriora-

tion of the swallowing disorders, under certain circumstances it may even result in aspiration. The use of the magnet for temporary interruption of the stimulation during meals may reduce the risk for aspiration [300].

## Acknowledgments

The authors thank Dr. **Steffen Fetzer,** LivaNova Deutschland GmbH, Munich, for his favorable advices and valuable discussions concerning technical questions, the manuscript and drawings.

## Conflict of Interest

Dr. H. Möbius was supported by Inspire medical Company with the payment of travel expenses for a surgery course.

## References

[1] Jacoby A, Snape D, Baker G. Epilepsy and social identity. The stigma of a chronic neurological disorder. The Lancet Neurology 2005; 4: 171–178

[2] Pohlmann-Eden B, Beghi E, Camfield C, Camfield P. The first seizure and its management in adults and children. In BMJ (Clinical research ed.) 2006; 332: 339–342

[3] Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994; 35: 1–6

[4] Fisher R, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017; 58: 531–542

[5] Cordes N. Invasive vs. transkutane Vagusnervstimulation: Ein Vergleich beider Stimulationsarten hinsichtlich Effizienz sowie lebensqualitativer Aspekte bei therapierefraktärer Epilepsie-Untersuchungen durch das Epilepsiezentrum Marburg. Dissertation Marburg 2019 http://archiv.ub.uni-marburg.de/diss/z2019/0434/pdf/dnc.pdf

[6] Schneider F et al. S3-Leitlinie/Nationale VersorgungsLeitlinie, Unipolare Depression, Kurzfassung, 2 Aufl. 2017; Version 1 AWMF-Register-Nr.: nvl-005

[7] Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998; 33: 587–595

[8] Ebmeier KP, Donaghey C, Steele JD. Recent developments and current controversies in depression. Lancet 2006; 367: 153–167

[9] Schneider F et al. S3-Leitlinie/Nationale VersorgungsLeitlinie, Unipolare Depression, Kurzfassung. 2 Aufl 2017 Version 1 AWMF-Register-Nr.: nvl-005

[10] Elger CE, Berkenfeld R et al. S1-Leitlinie Erster epileptischer Anfall und Epilepsien im Erwachsenenalter. 2017. Deutsche Gesellschaft für Neurologie, Hrsg. Leitlinien für Diagnostik und Therapie in der Neurologie.Online: www.dgn.org/leitlinien (abgerufen am 24.08.2021) AWMF-Register-Nr.: 030-041.

[11] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy. A review. Acta neurologica Belgica 2016; 116: 241–248

[12] Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51: 1069–1077

[13] Yuen AWC, Sander JW. Can natural ways to stimulate the vagus nerve improve seizure control? Epilepsy & behavior: E&B 2017; 67: 105–110

[14] Zanchetti A, Wang SC, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalography and clinical neurophysiology 1952; 4: 357–361

[15] Chase MH, Nakamura Y, Clemente CD, Sterman MB. Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. Brain Research. Elsevier; 1967: 5: 236–249

[16] Lockard JS, Congdon WC, DuCharme LL. Feasibility and Safety of Vagal Stimulation In Monkey Model. Epilepsia 1990; 31: 20–26

[17] Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia 1990; 31: 7–19

[18] McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia 1993; 34: 918–923

[19] Fernandez-Guardiola A, Martinez A, Valdes-Cruz A. Vagus nerve prolonged stimulation in cats: effects on epileptogenesis (amygdala electrical kindling): behavioral and electrographic changes. Epilepsia 1999; 40: 822–829

[20] Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia. 1992; 33: 1005–1012

[21] Penry JK, Dean IC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: Preliminary results [abstract]. Epilepsy 1990; 31: 40–43

[22] Rutecki P. Anatomical, physiological and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia. 1990; 31: 1–6

[23] Uthman BM, Wilder BJ, Penry JK, Dean C, Ramsay RE, Reid S et al. Treatment of epilepsy by stimulation of the vagus nerve. Neurology 1993; 43: 1338–1345

[24] Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01–E05. Neurology 1999; 53: 1731–1735

[25] Elger G et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000; 42: 203–210

[26] Sackeim HA et al. Vagus Nerve Stimulation (VNS™) for Treatment-Resistant Depression: Efficacy, Side Effects, and Predictors of Outcome. Neuropsychopharmacology 2001; 25: 713–728

[27] Rush AJ et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005; 58: 347–354

[28] Bajboui M, Merkl A et al. Two-Year Outcome of Vagus Nerve Stimulation inTreatment-Resistant Depression. Journal of Clinical Psychopharmacology 2010; 30: 273–281

[29] Aaronson ST, Sears P, Ruvuna F et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. American Journal of Psychiatry 2017; 174: 640–648

[30] Feldman RL, Dunner DL, Muller JS, Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. J Med Econ 2013; 16: 62–74

[31] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy. A review. In: Acta neurologica Belgica 2016; 116: 241–248

[32] Yuen AWC, Sander JW. Can natural ways to stimulate the vagus nerve improve seizure control? In: Epilepsy & behavior: E&B 2017; 67: 105–110

[33] Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure. Results of the ANTHEM-HF trial. Journal of cardiac failure 2014; 20: 808–816

[34] Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. In: Expert review of neurotherapeutics 2007; 7: 1763–1773

[35] PLC LivaNova, London, UK VNS Therapy System Epilepsy, Physician's Manual (OUS), August 2020

[36] Howland RH. New developments with vagus nerve stimulation therapy. Journal of psychosocial nursing and mental health services 2014; 52: 11–14

[37] Bertolini R, Leutert G. Systematische Anatomie des Menschen. Verlag Volk und Gesundheit 1987; 3: 431–435

[38] Hirsch M, Reinacher P, Schulze-Bonhage A. Vagusnervstimulation in der Behandlung von Epilepsiepatienten. Aktuelle Neurologie 2016; 43: 501–510. doi:10.1055/s-0042-116022

[39] Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex – linking immunity and metabolism. Nat. Rev. Endocrinol 2012; 8: 743–754. doi:10.1038/nrendo.2012.189

[40] Camara R, Griessenauer CJ. Anatomy of the Vagus Nerve. Nerves and Nerve Injuries 2015; 1: 385–397

[41] Thompson N, Mastitskaya S, Holder D. Avoiding off-target effects in electrical stimulation of the cervical vagus nerve: neuroanatomical tracing techniques to study fascicular anatomy of the vagus nerve. Journal of Neuroscience Methods 2019; 325: 108325. doi:10.1016/j.jneumeth.2019.108325

[42] Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol 2016; 594: 5781–5790. doi:10.1113/JP271539

[43] Standring S et al. Gray´s Anatomy. The Anatomical Basis of Clinical Practice. 42. Ed. Elsevier Limited; 2021

[44] Oliveira THF, Francisco AN, Demartini Z, Stebel SL. The role of vagus nerve stimulation in refractory epilepsy. Arquivos de neuro-psiquiatria 2017; 75: 657–666

[45] Ekmekci H, Kaptan H. Vagus Nerve Stimulation. Open access Macedonian journal of medical sciences 2017; 5: 391–394

[46] Camara R, Griessenauer CJ. Chapter 27 – Anatomy of the Vagus Nerve. Nerves and Nerve Injuries.Elsevier Ltd; 2015: Vol. 1: 385–397. doi:10.1016/B978-0-12-410390-0.00028-7

[47] Shiozawa P. Vagus nerve stimulation in neuropsychiatry. Targeting anatomy-based stimulation sites. Epilepsy & behavior: E&B 2015; 51: 18

[48] Verlinden TJM, Rijkers K, Hoogland G, Herrler A. Morphology of the human cervical vagus nerve: implications for vagus nerve stimulation treatment. Acta Neurol. Scand 2016; 133: 173–182. doi:10.1111/ane.12462)

[49] Beckett EAH, Sanders KM, Ward SM. Inhibitory responses mediated by vagal nerve stimulation are diminished in stomachs of mice with reduced intramuscular interstitial cells of Cajal. Sci Rep 2017; 7: 44759. doi:10.1038/srep44759

[50] Shiozawa P. Vagus nerve stimulation in neuropsychiatry. Targeting anatomy-based stimulation sites. Epilepsy & behavior: E&B 2015; 51: 18

[51] Gasser HS, Grundfest H. Axon diameters in relation to the spike dimensions and the conduction velocity in mammalian A fibers. Am J Physiol 1939; 127: 393–414

[52] Krahl SE, Senanayake SS, Handforth A. Destruction of peripheral C-fibers does not alter subsequent vagus nerve stimulation-induced seizure suppression in rats. Epilepsia 2001; 42: 586–589

[53] Penry JK, Dean IC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: Preliminary results [abstract]. Epilepsy 1990; 31: 40–43

[54] Bailey P, Bremer F. A sensory cortical representation of the vagus nerve (with a note on the effects of low blood pressure on the cortical electrograms). J Neurophysiol 1938; 1: 405–412

[55] MacLean PD. The Triune Brain in Evolution: Role in Paleocerebral Functions. New York: Plenum Press; 1990. doi:10.1126/science.250.4978.303-a

[56] Dell P, Olson R. Projections 'secondaires' mesencephaliques, diencephaliques et amygdaliennes des afferences viscerales vagales. C R Soc Biol 1951; 145: 1088–1091

[57] Zabara J. Peripheral control of hypersynchronous discharge in epilepsy. Electroencephalogr Neu-rophysiol 1985; 61: 162

[58] Hermanowicz N. Chapter 13 – cranial nerves IX (glossopharyngeal) and X (vagus). Textbook of clinical neurology 2007; 217–229. doi:10.1016/B978-141603618-0.10013-X

[59] Monkhouse S. 15 – The vagus nerve (X). Cambridge University Press; 2006: 86–91. doi:10.1017/CBO9780511543524.016

[60] Camara R, Griessenauer CJ. Anatomy of the Vagus Nerve. Nerves and Nerve Injuries 2015; 1: 385–397. doi:10.1016/B978-0-12-410390-0.00028-7

[61] Gilman S, Chervin RD, Koeppe RA, Consens FB, Little R. Junck L. Heumann. Obstructive sleep apnea is related to a thalamic cholinergic deficit in MSA. Neurology 2003; 61: 35–39. Neurology 2003; 61: 35–39

[62] Hachem LD, Wong SM, Ibrahim GM. The vagus afferent network: emerging role in translational connectomics. Neurosurg Focus 2018; 45: 1–8. doi:10.3171/2018.6.FOCUS18216

[63] George MS, Sackeim HA et al. Vagus nerve stimulation: A new tool for brain research and therapy. Biol Psychiatry 2000; 47: 287–295

[64] George MS, Sackeim HA et al. Vagus nerve stimulation. A potential therapy for resistant depression? Psych Clin North Am 2000; 23: 757–783

[65] Rush AJ, Linden M, Zobel A. Vagus Nerve Stimulation. A Potential Therapy for Chronic/Recurrent Depression? Fortschritte der Neurologie • Psychiatrie 2002; 70: 297–302. doi:10.1055/s-2002-32022

[66] Van Bockstaele EJ, Peoples J et al. Anatomic basis for differential regulation of the rostrolateral pen-locus coeruleus region by limbic afferents. Biol Psychiatry 1999; 46: 1352–1363

[67] Ricardo JA, Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures. Brain Res 1978; 152: 1–10

[68] Otterson OP. Afferent connection to the amygdaloin complex of the rat with some observations in the cat. III. Afferents from lower brainstem. J Comp Neurol 1981; 202: 335

[69] Zardetto-Smith AM, Gray TS. Organization of peptidergic and catecholaminergic efferents from the nucleus of the solitary tract to the rat amygdala. Brain Res Bull 1990; 25: 875

[70] Van der Kooy D, Koda LY, McGinty JF, Gerfen CR, Bloom FE. The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in the rat. J Comp Neurol 1984; 224: 1–20

[71] Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure attenuating effects of vagus nerve stimulation. Epilepsia 1998; 39: 709–714

[72] Henry TR. Therapeutic mechanisms of vagus nerve stimulation. In: Neurology 2002; 59: 3–14

[73] Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart – a novel model of isolated langendorff perfused rabbit heart with intact dual autonomic innervation. Exp. Physiol 2001; 86: 319–329. doi:10.1113/eph8602146

[74] Yoo PB, Liu H, Hincapie JG, Ruble SB, Hamann JJ, Grill WM. Modulation of heart rate by temporally patterned vagus nerve stimulation in the anesthetized dog. Physiol. Rep 2016; 4: 12689. doi:10.14814/phy2.12689

[75] Tekdemir I, Aslan A, Elhan A. A clinico-anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reflex. Surg Radiol Anat 1998; 20: 253–257

[76] Leblanc A. Anatomy and Imaging of the Cranial Nerves, A Neuroanatomic Method of Investigation Using Magnetic Resonance Imaging (MRI) and Computed Tomography (CT). Springer; Berlin Heidelberg, Berlin, Heidelberg: 1992: 1 241–250. doi:10.1007/978-3-642-97042-9

[77] Reidler PL. Einfluss der transkutanen Vagusnervstimulation auf die funktionelle Konnektivität bei chronischen Schmerzpatienten: Eine fMRT-basierte Pilotstudie. Dissertation München. 2019;https://edoc.ub.unimuenchen.de/24617/1/Reidler_Paul.pdf

[78] Nomura S, Mizuno N. Central distribution of primary afferent fibers in the Arnold's nerve (the auricular branch of the vagus nerve): A transganglionic HRP study in the cat. Brain Res 1984; 292: 199–205. doi:10.1016/0006-8993(84)90756-X

[79] Walker BR, Easton A, Gale K. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. Epilepsia 1999; 40: 1051–1057

[80] Raedt R, Clinckers R, Mollet L et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. J Neurochem 2011; 117: 461–469

[81] Nahas Z, Teneback C, Chae JH, Mu Q, Molnar C, Kozel FA, Walker J, Anderson B, Koola J, Kose S, Lomarev M, Bohning DE, George MS. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. Neuropsychopharmacol 2007; 32: 1649–1660. doi:10.1038/sj.npp.1301288

[82] Zhu J, Xu C, Zhang X, Qiao L, Wang X, Zhang X, Yan X, Ni D, Yu T, Zhang G, Li Y. A resting-state functional MRI study on the effect of vagal nerve stimulation on spontaneous regional brain activity in drug-resistant epilepsy patients. Behav Brain Res 2020; 392: 112709. doi:10.1016/j.bbr.2020.112709

[83] Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, George MS, Charney DS, Brannan SK. VNS therapy in treatmentresistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacol 2006; 31: 1345–1355. doi:10.1038/sj.npp.1301082

[84] Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B, Johnson KA, Denslow S, Lomarev M, Moghadam P, Chae JH, George MS. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. Biol Psychiatry 2004; 55: 816–825. doi:10.1016/j.biopsych.2003.12.004

[85] Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. J Psychiatr Res 2002; 36: 219–227. doi:10.1016/s0022-3956(02)00013-4

[86] Smith LJ, Rosen CA, Niyonkuru C, Munin MC. Quantitative electromyography improves prediction in vocal fold paralysis. The Laryngoscope 2012; 122: 854–859

[87] Koopman FA, Tang MW, Vermeij J, de Hair MJ, Choi IY, Vervoordeldonk MJ et al. Autonomic dysfunction precedes development of rheumatoid arthritis: a prospective cohort study. EBioMedicine 2016; 6: 231–237. doi:10.1016/j.ebiom.2016.02.029

[88] Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol 2016; 594: 5781–5790. doi:10.1113/JP271539

[89] Bonaz B, Sinniger V, Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. J Intern Med 2017; 282: 46–63. doi:10.1111/joim.12611

[90] Fisher RS, Eggleston KS, Wright CW. Vagus nerve stimulation magnet activation for seizures: A critical review. Acta Neurol Scand 2014; 131: 1–8. doi:10.1111/ane.12288

[91] Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 2002; 1: 477–482

[92] Handforth A, DeGiorgio CM, Schachter SC et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998; 51: 48–55

[93] Kahlow H, Olivecrona M. Complications of vagal nerve stimulation for drug-resistant epilepsy: a single center longitudinal study of 143 patients. Seizure 2013; 22: 827–833

[94] Tatum WO, Moore DB, Stecker MM et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology 1999; 52: 1267–1269

[95] Ardesch JJ, Buschman HPJ, van der Burgh PH et al. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. Clin Neurol Neurosurg 2007; 109: 849–852

[96] Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society 2001; 18: 415–418

[97] Gandhi H, Ippoliti M, Iqbal F, Shah A. Bradyarrhythmia secondary to vagus nerve stimulator 7 years after placement. BMJ Case Rep 2020; 13: e235514. doi:10.1136/bcr-2020-235514

[98] Spuck S, Tronnier V, Orosz I, Schönweiler R et al. Operative and technical complications of vagus nerve stimulator implantation. Neurosurgery. 2010; 67: 489–494. doi:10.1227/NEU.0b013e3181f88867

[99] Revesz D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr 2016; 18: 1–8. doi:10.3171/2016.1.PEDS15534

[100] Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01–E05. Neurology 1999; 53: 1731–1735

[101] Morris GL, Gloss D, Buchhalter J et al. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013; 81: 1453–1459. doi:10.1212/WNL.0b013e3182a393d1

[102] Elliott RE, Morsi A, Kalhorn SP, Marcus J et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: Long-term outcomes and predictors of response. Epilepsy & Behavior 2011; 20: 57–63

[103] Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy & Behavior 2017; 66: 4–9

[104] Orosz I, McCormick D, Zamponi N, Varadkar S et al. Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. Epilepsia 2014; 55: 1576–1584

[105] Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol 2001; 18: 415–418

[106] Parhizgar F, Nugent K, Raj R. Obstructive sleep apnea and respiratory complications associated with vagus nerve stimulators. J Clin Sleep Med 2011; 7: 401–407

[107] Hsieh T, Chen M, McAfee A et al. Sleep-related breathing disorder in children with vagal nerve stimulators. Pediatr Neurol 2008; 38: 99–103

[108] Grigg-Damberger M, Foldvary-Schaefer N. Bidirectional relationships of sleep and epilepsy in adults with epilepsy. Epilepsy & Behavior 2021; 116: 107735. doi:10.1016/j.yebeh.2020.107735

[109] Malow BA, Edwards J, Marzec M et al. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. Neurology 2000; 55: 1450–1454

[110] Marzec M, Edwards J, Sagher O et al. Effects of vagus nerve stimulation on sleep-related breath-ing in epilepsy patients. Epilepsia 2003; 44: 930–935

[111] Gschliesser V, Högl B, Frauscher B et al. Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy. Seizure 2009; 18: 339–342

[112] Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol 2010; 27: 130–138

[113] Helmers SL et al. Acta Neurol. Scand 2012; Heck C et al. Neurology 2002; 59: 31–37

[114] Thompson SL, O´Leary G, Austelle CW et al. A Review of Parameter Settings for Invasive and Non-invasive Vagus Nerve Stimulation (VNS) Applied in Neurological and Psychiatric Disorders. Front. Neurosci 2021; 15: 1–14. doi:10.3389/fnins.2021.709436

[115] Smith CD, Geddes LA, Bourland JD, Foster KS, Schoenlein WE. The chronaxie and propagation velocity of canine cervical vagus nerve fibers in vivo. Cardiovasc Eng 2001; 1: 77–84

[116] Helmers SL, Begnaud J, Cowley AW, Corwin HM, Edwards JC, Holder DL et al. Application of a computational model of vagus nerve stimulation. Acta Neurol Scand 2012; 126: 336–343

[117] Castoro MA, Yoo PB, Hincapie JG et al. Excitation properties of the right cervical vagus nerve in adult dogs. Exp Neurol 2011; 227: 62–8.19

[118] El Tahry R, Mollet L, Raedt R et al. Repeated assessment of larynx compound muscle action potentials using a self-sizing cuff electrode around the vagus nerve in experimental rats. J Neurosci Methods 2011; 198: 287–293

[119] Koo B, Ham SD, Sood S et al. Human vagus nerve electrophysiology: a guide to vagus nerve stimulation parameters. J Clin Neurophysiol 2001; 18: 429–433

[120] Evans MS, Verma-Ahuja S, Naritoku DK et al. Intraoperative human vagus nerve compound action potentials. Acta Neurol Scand 2004; 110: 232–238

[121] Woodbury JW, Woodbury DM. Vagal stimulationreduces the severity of maximal electroshock seizures in intact rats: use of a cuff electrode for stimulating and recording. Pace 1991; 14: 94–107 1991

[122] Krahl SE, Senanayake SS, Handforth A. Destruction of peripheral c-fibers does not alter subse-quent vagus nerve stimulation-induced seizure suppression in rats. Epilepsia 2001; 42: 586–589

[123] Koo B, Ham SD, Sood S, Tarver B. Human Vagus Nerve Electrophysiology A Guide to Vagus Nerve Stimulation Parameters. Journal of Clinical Neurophysiology 2001; 18: 429–433

[124] Helmers SL, Begnaud J, Cowley AW, Corwin HM, Edwards JC, Holder DL et al. Application of a computational model of vagus nerve stimulation. Acta Neurol Scand 2012; 126: 336–343

[125] Fisher B, DesMarteau J, Koontz E, Wilks S, Melamed S. Responsive Vagus Nerve Stimulation for Drug Resistant Epilepsy: A Review of New Features and Practical Guidance for Advanced Practice Providers. Frontiers in Neurology 2021; 11: 1–10. doi:10.3389/fneur.2020.610379

[126] Gurbani SG, Mittal M, Gurbani N et al. Efficacy of rapid cycling vagus nerve stimulation in pharmaco-resistant epilepsy. Neurology Asia 2004; 9: 131

[127] Kayyali H et al. The Efficacy and Safety of Rapid Cycling Vagus Nerve Stimulation in Children with Intractable Epilepsy. Pediatric Neurology 2020; 109: 35–38

[128] O´Reardon JP et al. A case study of refractory major depression with a delayed response to vagus nerve stimulation (vns): optimizing the duty cycle to improve efficacy. Depression: Mind and Body 2006; 3: 32–34

[129] Larsen LE, Wadman WJ, Marinazzo D, van Mierlo P et al. Vagus Nerve Stimulation applied with a rapid cycle has more profound influence on hippocampal electrophysiology than a standard cycle. Neurotherapeutics 2016; 13: 592–602. doi:10.1007/s13311-016-0432-8

[130] Gurbani SG, Mittal M, Gurbani N et al. Efficacy of rapid cycling vagus nerve stimulation in pharmaco-resistant epilepsy. Neurology Asia 2004; 9: 131

[131] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy. A review. Acta neurologica Belgica 2016; 116: 241–248

[132] Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B et al. Acute Vagus Nerve Stimulation Using Different Pulse Widths Produces Varying Brain Effects. BIOL PSYCHIATRY 2004; 55: 816–825. doi:10.1016/j.biopsych.2003.12.004

[133] Boon P, Vonck K, van Walleghem P et al. Programmed and magnetinduced vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 2001; 18: 402–407

[134] Morris GL. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. Epilepsy Behav 2003; 4: 740–745

[135] Chouchou F, Bouet R, Pichot V et al. The neural bases of ictal tachycardia in temporal lobe seizures. Clin Neurophysiol 2017; 128: 1810–1819. doi:10.1016/j.clinph.2017.06.033

[136] Eggleston KS, Olin DO, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure 2014; 23: 496–505

[137] Hirsch M, Altenmüller DM, Schulze-Bonhage A. Latencies from intracranial seizure onset to ictal tachycardia: A comparison to surface EEG patterns and other clinical signs. Epilepsia 2015; 56: 1639–1647

[138] Leutmezer F, Schernthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. Epilepsia 2003; 44: 348–354

[139] Boon P, Vonck K, van Rijckevorsel K et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 2015; 32: 52–61

[140] El Tahry R, Hirsch M, Van Rijckevorsel K et al. Early experiences with tachycardia-triggered vagus nerve stimulation using the AspireSR stimulator. Epileptic Disord 2016; 18: 155–162

[141] Bialer M et al. Seizure detection and neuromodulation: A summary of data presented at the XIII conference on new antiepileptic drug and devices (EILAT XIII). Epilepsy Research 2017; 130: 27–36

[142] Hampel KG, Vatter H, Elger CE et al. Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy. Seizure 2015; 26: 81–85

[143] Ravan M, Sabesan S et al. On Quantitative Biomarkers of VNS Therapy Using EEG and ECG Signals. Transactions on Biomedical Engineerig 2017; 64: 419–428

[144] Page T, Fergus J, Rugg-Gunn FJ. Bitemporal seizure spread and its effect on autonomic dysfunction. Epilepsy & Behavior 2018; 84: 166–172

[145] Ryvlin P, So EL, Gordon CM, Hesdorffer DC et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018; 59: 562–572

[146] Ventureyra EC. Transcutaneous vagus nerve stimulation for partial onset seizure therapy. A new concept. In: Child's nervous system: ChNS: official journal of the International Society for Pediatric Neurosurgery 2000; 16: 101–102

[147] Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: A proof of concept trial. Epilepsia 2012; 53: 115–118

[148] Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin. Anat. 2002; 15: 35–37. doi:10.1002/ca.1089

[149] Hecker H, Steveling A, Peuker E. Lehrbuch und Repititorium Ohr-, Schädel-, Mund- Hand-Akupunktur. 3. Aufl 2002 Hippokrates Verlag;Stuttgart: S.7

[150] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review. Part II. Headache 2016; 56: 259–266

[151] Bauer S, Baier H, Baumgartner C et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02). Brain Stimulation 2016; 9: 356–363

[152] Rong PJ, Liu AH et al. Transcutaneous vagus nerve stimulation for refractory epilepsy: a random-ized controlled trial.Portland Press; 2014 Clin Sci (Lond) 2014; CS20130518. doi:10.1042/CS20130518

[153] Fallgatter AJ, Neuhauser B, Herrmann MJ et al. Far field potentials from the brain stem after transcutaneous vagus nerve stimulation. J Neural Transm 2003; 110: 1437–1443

[154] Kraus T, Hosl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm 2007; 114: 1485–1493

[155] Dietrich S, Smith J, Scherzinger C et al. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. Biomed Tech (Berl) 2008; 53: 104–111

[156] Howland Robert H. New developments with vagus nerve stimulation therapy. Journal of psychosocial nursing and mental health services 2014; 52: 11–14

[157] Farmer AD, Strzelczyk A, Finiguerra A et al. International Consensus Based Review and Recom-mendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020). Front Hum Neurosci 2021; 14: 1–47. doi:10.3389/fnhum.2020.568051

[158] Clancy JA, Deuchars SA, Deuchars J. The wonders of the Wanderer. Exp. Physiol 2013; 98: 38–45. doi:10.1113/expphysiol.2012.064543

[159] Chakravarthy K, Chaudhry H, Williams K, Christo PJ. Review of the Uses of Vagal Nerve Stimulation in Chronic Pain Management. Curr. Pain Headache Rep 2015; 19: 54. doi:10.1007/s11916-015-0528-6

[160] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part II. Headache 2016; 56: 259–266. doi:10.1111/head.12650

[161] Kreuzer PM, Landgrebe M et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Front Psychiatry 2012; 3: 70. doi:10.3389/fpsyt.2012.00070

[162] Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies. A proof of concept trial. Epilepsia 2012; 53: 115–118

[163] Bauer S, Baier H, Baumgartner C, Bohlmann K, Fauser S, Graf W et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug- Resistant Epilepsy. A Randomized, Double-Blind Clinical Trial (cMPsE02). Brain stimulation 2016; 9: 356–363

[164] Schulze-Bonhage A. Brain stimulation as a neuromodulatory epilepsy therapy. Seizure 2017; 44: 169–175

[165] Mertens A, Raedt R, Gadeyne S, Carrette E, Boon P, Vonck K. Recent advances in devices for vagus nerve stimulation. Expert Rev Med Devices 2018; 15: 527–539

[166] De Couck M, Cserjesi R, Caers R, Zijlstra WP, Widjaja D, Wolf N et al. Effects of short and pro-longed transcutaneous vagus nerve stimulation on heart rate variability in healthy subjects. Auton Neurosci 2017; 203: 88–96

[167] Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. J. Cardiac Failure 2014; 20: 808–816

[168] Wang Z, Zhou X, Sheng X, Yu L, Jiang H. Noninvasive vagal nerve stimulation for heart failure: was it practical or just a stunt. Int J Cardiol 2015; 187: 637–638

[169] www.bundesanzeiger.de/pub/de/amtlicher-teil?0&year = 2017&edition = BAnz + AT + 16.10.2017

[170] Yap JYY et al. Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice. Front Neurosci 2020; 14: 284

[171] www.gammacore.com/wp-content/uploads/2021/02/gammaCore-Sapphire-IFU.pdf

[172] Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia 2014; 34: 986–993

[173] Nesbitt AD, Marin JCA, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology 2015; 84: 1249–1253

[174] https://edoc.ub.uni-muenchen.de/24617/1/Reidler_Paul.pdf

[175] Farmer AD, Strzelczyk A, Finiguerra A et al. International Consensus Based Review and Recom-mendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020). Front Hum Neurosci 2021; 14: 1–47. doi:10.3389/fnhum.2020.568051

[176] Kampusch S, Kaniusas E, Széles JC.2013: “New approaches in multi-punctual percutaneous stimulation of the auricular vagus nerve,” in 2013 6th International IEEE/EMBS Conference on Neural Engineering (NER). San Diego, CA: 263–266. doi:10.1109/NER.2013.6695922

[177] Englot DJ, Rolston JD et al. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery 2016; 79: 345–353

[178] Renfroe J, Wheless JW. Earlier use of adjunctive vagus nerve stimulation Therapy for refractory epilepsy. Neurology 2002; 59: 26–30

[179] Brazdil M, Dolezalova I et al. EEG Reactivity Predicts Individual Efficacy of Vagal Nerve Stimulation in Intractable Epileptics. Frontiers in Neurology 2019; 10: 392. doi:10.3389/fneur.2019.00392

[180] Babajani-Feremia A, Noorizadeh N et al. Predicting seizure outcome of vagus nerve stimulation using MEG-based network topology. NeuroImage 2018; 19: 990–999

[181] Xiong J, Cao Y et al. Can we predict response to vagus nerve stimulation in intractable epilepsy. Int J Neurosience 2020; 130: 1063–1070. doi:10.1080/00207454.2020.1713777

[182] Lagae L, Verstrepen A, Nada A et al. Vagus nerve stimulation in children with drug-resistant epi-lepsy: age at implantation and shorter durationof epilepsy as predictors of better efficacy? Epileptic Disorders 2015; 17: 308–314

[183] Mithani K, Mikhail M, Morgan BR et al. Connectomic Profiling Identifies Responders to Vagus Nerve Stimulation. Annals Neurol 2019; 743–753. doi:10.1002/ana.25574

[184] Ghaemi K, Elsharkawy AE, Schulz R, Hoppe M, Polster T, Pannek H, Ebner A. Vagus nerve stimulation: outcome and predictors of seizure freedom in long-term follow-up. Seizure 2010; 19: 264–268

[185] Janszky J, Hoppe M, Behne F, Tuxhorn I, Pannek HW, Ebner A. Vagus nerve stimulation: predictors of seizure freedom. J Neurol Neurosurg Psychiatry 2005; 76: 384–389

[186] Bodin C et al. Responders to Vagus Nerve Stimulation (VNS) in refractory epilepsy have reduced interictal cortical synchronicity on scalp EEG. Epilepsy Res 2015; 113: 98–103

[187] Schulze-Bonhage A, Hamer HM, Hirsch M et al. Invasive Stimulationsverfahren und EEG-Diagnostik bei Epilepsien. Nervenarzt 2016; 87: 829–837

[188] Möddel G, Coenen VA, Elger CE. Invasive Neurostimulation in der Epilepsietherapie. Der Nervenarzt 2012; 83: 1001–1005

[189] The Vagus Nerve Stimulation Study Group A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995; 45: 224–230

[190] Handforth A, DeGiorgio CM, Schachter SC et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998; 51: 48–55

[191] Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999; 53: 666–669

[192] Klinkenberg S, Aalbers MW, Vles JS et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol 2012; 54: 855–861

[193] Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01–E05. Neurology 1999; 53: 1731–1735

[194] Tatum WO, Johnson KD, Goff S et al. Vagus nerve stimulation and drug reduction. Neurology 2001; 56: 561–563

[195] McHugh JC, Singh HW, Phillips J et al. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 2007; 48: 375–378

[196] Orosz I, McCormick D, Zamponi N et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 2014; 55: 1576–1584

[197] Englot DJ, Rolston JD, Wright CW et al. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable Epilepsy. Neurosurgery 2015; 79: 345–353

[198] Montavont A, Demarquay G, Ryvlin P et al. Efficacité de la stimulation intermittente du nerf vague dans les épilepsies pharmaco-résistantes non chirurgicales de l'adolescent et de l'adulte. Revue neurologique 2007; 163: 1169–1177

[199] Alexopoulos AV, Kotagal P, Loddenkemper T et al. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 2006; 15: 491–503

[200] Ardesch JJ, Buschman HPJ, Wagener-Schimmel LJJC, van der Aa HE, Hageman G. Vagus nerve stimulation for medically refractory epilepsy. A long-term follow-up study. Seizure 2007; 16: 579–585

[201] Hamilton P et al. Clinical outcomes of VNS therapy with AspireSR (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure 2018; 58: 120–126. doi:10.1016/j.seizure.2018.03.022

[202] Data P, Galla K, Sajja K, Wichman C, Wang H, Madhavan D. Vagus nerve stimulation with tachycardia detection provides additional seizure reduction compared to traditional vagus nerve stimulation. Epilepsy & Behavior 2020; 111: 107280. doi:10.1016/j.yebeh.2020.107280

[203] Dibue M, Greco T, Spoor JKH, Tahir Z, Specchio N, Hänggi D, Steiger H, Kamp M. Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: A meta-analysis. Acta Neurol Scand 2020; 143: 497–508. doi:10.1111/ane.13375

[204] Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. Epilepsia 1998; 39: 206–212

[205] Tatum WO, Vale FL. Vagus nerve stimulation and cardiac asystole. Epilepsia 2009; 50: 2671–2672

[206] Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Time trends in incidence, mortality, and case-fatality after first episode of status epilepticus. Epilepsia 2001; 42: 1031–1035

[207] Stelzer FG, Bustamante G, Sander H et al. Short-term mortality and prognostic factors related to status epilepticus. Arq. Neuro-Psiquiatr. 2015; 73: 670–675. doi:10.1590/0004-282X20150082

[208] Helmers SL, Duh MS, Guerin A et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paedriatr Neurol 2012; 16: 449–458

[209] Dibue-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus e A systematic review. 2019. Brain Stimulation. 2019: 12: 1101–1110 Elsevier Inc; doi:10.1016/j.brs.2019.05.011

[210] Ryvlin P, Gilliam FG, Nguyen DK et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia 2014; 55: 893–900

[211] Schulze-Bonhage A, Hamer HM, Hirsch M et al. Invasive Stimulationsverfahren und EEG-Diagnostik bei Epilepsien. Nervenarzt 2016; 87: 829–837. doi:10.1007/s00115-016-0159-0

[212] Baumgartner C. Eine kritische Bilanz. Neurostimulation in epilepsy treatment. A critical review Nervenheilkunde.2007: Schattauer GmbH; 26 999–1005. doi:10.1055/s-0038-1626953

[213] Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol 2001; 18: 415–418

[214] Ekmekci H, Kaptan H. Vagus Nerve Stimulation. Open access Macedonian journal of medical sciences 2017; 5: 391–394

[215] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy. A review. Acta neurologica Belgica 2016; 116: 241–248

[216] Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. Expert review of neurotherapeutics 2007; 7: 1763–1773

[217] Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. Epilepsy & behavior: E&B 2003; 4: 302–309

[218] Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 1999; 53: 1731

[219] Hermann BP, Trenerry MR, Colligan RC. Learned helplessness, attributional style, and depression in epilepsy. Bozeman Epilepsy Surgery Consortium. Epilepsia 1996; 37: 680–686

[220] Huf RL, Mamelak A, Kneedy-Cayem K. Vagus nerve stimulation therapy. 2-year prospective open-label study of 40 subjects with refractory epilepsy and low IQ who are living in long-term care facilities. Epilepsy & behavior: E&B 2005; 6: 417–423

[221] Wasade VS, Schultz L, Mohanarangan K, Gaddam A, Schwalb JM, Spanaki-Varelas M. Long-term seizure and psychosocial outcomes of vagus nerve stimulation for intractable epilepsy. Epilepsy & behavior: E&B 2015; 53: 31–36

[222] Carius A, Wintermantel A. Vagusnervstimulationstherapie bei Epilepsiepatienten. Langzeitoutcome und Nebenwirkungen: eine retrospektive Analyse. In: Der Nervenarzt 2013; 84: 1473–1485

[223] Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation. Clinical experience in a large patient series. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society 2001; 18: 408–414

[224] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy research 2000; 42: 203–210

[225] Klinkenberg S, Majoie HJM, van der Heijden MM, Rijkers K, Leenen L, Aldenkamp AP. Vagus nerve stimulation has a positive effect on mood in patients with refractory epilepsy. Clinical neurology and neurosurgery 2012; 114: 336–340

[226] Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation. Clinical experience in a large patient series. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society 2001; 18: 408–414

[227] Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. Epilepsy & behavior: E&B 2001; 2: 46–53

[228] Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy. Effect on health care utilization. Epilepsy & behavior: E&B 2007; 10: 134–137

[229] Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 2006; 15: 491–503

[230] McLachlan RS, Sadler M, Pillay N, Guberman A, Jones M et al. Quality of life after vagus nerve stimulation for intractable epilepsy. Is seizure control the only contributing factor? European neurology 2003; 50: 16–19

[231] Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. In: Epilepsy & behavior: E&B 2003; 4: 302–309

[232] Olin B, Javewardene A, Bunker M, Moreno F. Mortality and Suicide Risk in Treatment-Resistant Depression: An Observational Study of the Long-Term Impact of Intervention. plos one 2012; 7: 48002. doi:10.1371/journal.pone.0048002

[233] Schulze-Bonhage A, Hamer HM, Hirsch M et al. Invasive Stimulationsverfahren und EEG-Diagnostik bei Epilepsien. Nervenarzt 2016; 87: 829–837. doi:10.1007/s00115-016-0159-0

[234] Stefan H, Kreiselmeyer G, Kerling F et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia 2012; 53: 115–118

[235] Bauer S, Baier H, Baumgartner C et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02). Brain Stimulation 2016; 9: 356–363

[236] Hermann S, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies. A proof of concept trial In: Epilepsia 2012; 53: 115–118

[237] Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy & behavior: E&B 2014; 39: 105–110

[238] Jacobs HIL, Riphagen JM, Razat CM et al. Transcutaneous vagus nerve stimulation boosts asso-ciative memory in older individuals. Neurobiol Aging 2015; 36: 1860–1867

[239] Morris GL. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. Epilepsy&behavior 2003; 4: 740–745

[240] Hermann S, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies. A proof of concept trial In: Epilepsia 2012; 53: 115–118

[241] Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy & behavior: E&B 2014; 39: 105–110

[242] Bauer S, Baier H, Baumgartner C, Bohlmann K, Fauser S, Graf W et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy. A Randomized, Double-Blind Clinical Trial (cMPsE02). Brain stimulation 2016; 9: 356–363

[243] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000; 42: 203–210

[244] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy. A review. Acta neurologica Belgica 2016; 116: 241–248

[245] Rush AJ, Marangell LB, Sackeim HA et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005; 58: 347–354

[246] Sackeim HA et al. Vagus Nerve Stimulation (VNS™) for Treatment-Resistant Depression: Efficacy, Side Effects, and Predictors of Outcome. Neuropsychopharmacology 2001; 25: 713–728

[247] Barth J, Schuhmacher M et al. Depression as a risk factor for mortality in patients with coronary heart desease. Psychosomatic med 2004; 66: 802–813

[248] Ladwig KH et al. Depression: Ein nach wie vor unterschätztes Risiko für die Entwicklung und Progressionder koronaren Herzerkrankung. Bundesgesundheitsblatt 2011; 54: 59–65

[249] Rosengren A, Hawken S, Ounpuu S, Sliwa K et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTER-HEART study): case-control study. The INTERHEART study. Lancet 2004; 364: 953–962

[250] Mende A. Das Herz leidet mit. Pharmazeutische Zeitung. 2011; 39:https://www.gbe-bund.de/gbe/abrechnung.prc_abr_test_logon?p_uid=gast&p_aid=0&p_knoten=FID&p_sprache=E&p_suchstring=701411

[251] Olin B, Javewardene A, Bunker M, Moreno F. Mortality and Suicide Risk in Treatment-Resistant Depression: An Observational Study of the Long-Term Impact of Intervention. PLOS ONE 2012; 7: e48002. doi:10.1371/journal.pone.0048002

[252] Hein E, Nowak M, Kiess O et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transmission (Vienna) 2013; 120: 821–827

[253] Kraus T, Hösl K, Kiess O et al. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transmission (Vienna) 2007; 114: 1485–1493

[254] Rong P, Liu J, Wang L et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. J Affect Disord 2016; 195: 172–179

[255] Trevizol AP, Shiozawa P, Taiar I et al. Transcutaneous vagus nerve stimulation (taVNS) for major depressive disorder: an open label proof-of-concept trial. Brain Stimul 2016; 9: 453–454

[256] Jacobs HIL, Riphagen JM, Razat CM et al. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiol Aging 2015; 36: 1860–1867

[257] Strzelczyk A, Griebel C, Lux W et al. The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data. Front Neurol 2017; 8: 712. doi:10.3389/fneur.2017.00712

[258] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. Headache 2016; 56: 71–78

[259] Verrier RL, Ikeda T. Ambulatory ECG-based T-wave alternans monitoring for risk assessment and guiding medical therapy: mechanisms and clinical applications. Prog Cardiovasc Dis 2013; 56: 172–185

[260] Zanobetti A, Stone PH, Speizer FE et al. T-wave alternans, air pollution and traffic in high-risk subjects. Am J Cardiol 2009; 104: 665–670

[261] Verrier RL, Nearing BD et al. Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. Epilepsy & Behavior 2016; 62: 85–89

[262] Strzelczyck A, Adjei P, Scott CA et al. Postictal increase in T-wave alternans after generalized tonic-clonic seizures. Epilepsia 2011; 52: 2112–2117

[263] Libbus I, Nearing BD, Amurthur B et al. Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the AN-THEM-HF study. Heart Rhythm 2016; 13: 721–728

[264] Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure. Results of the ANTHEM-HF trial. Journal of cardiac failure 2014; 20: 808–816

[265] https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00009292

[266] Benrath J, Hatzenbühler M, Fresenius M, Heck M. Kopf- und Gesichtsschmerz. Repetitorium Schmerztherapie. Springer; Berlin, Heidelberg: 2020: 1: 191–225. doi:10.1007/978-3-662-61783-0_9

[267] Diener HC, Gaul C, Kropp P et al. 2018; Therapie der Migräneattacke und Prophylaxe der Migräne, S1-Leitlinie. In: Deutsche Gesellschaft für Neurologie (Hrsg) Leitlinien für Diagnostik und Therapie in der Neurologie.https://dgn.org/leitlinien/3583-ll-030-057-2018-therapie-der-migraeneattacke-und-prophylaxe-der-migraene Zugegriffen: 22. Juni 2020.

[268] Kirchner A, Birklein F, Stefan H, Handwerker HO. Left vagus nerve stimulation suppresses experimentally induced pain. Neurology 2000; 55: 1167–1171

[269] Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception – an experimental study. Brain Stimul 2013; 6: 202–209

[270] Howland Robert H. New developments with vagus nerve stimulation therapy. Journal of psychosocial nursing and mental health services 2014; 52: S. 11–14

[271] Hord E, Evans M, Mueed S et al. The effect of vagus nerve stimulation on migraines. J Pain 2003; 4: 530–534

[272] Lenaerts M, Oommen K, Couch J et al. Can vagus nerve stimulation help mi-graine? Cephalalgia 2008; 28: 392–395

[273] Magis D, Gerard P, Schoenen J. Transcutaneous Vagus Nerve Stimulation (tVNS) for headache prophylaxis: initial experience. J Headache Pain 2013; 14: 198

[274] Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomized controlled study. Cephalalgia 2016; 36: 534–546

[275] Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia 2014; 34: 986–993

[276] 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. J Headache Pain 2015; 16: 543

[277] Diener H, Brössner G, Frank F, Holle D, Nägel S, Reuter U. Neues bei Migräne – Update 2021 Neurologie up2date 2021; 4: 195–214. doi:10.1055/a-1163-6539

[278] Diener HC, Goadsby PJ, Ashina M et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. Cephalalgia 2019; 39: 1475–1487

[279] Martelletti P, Jensen RH, Antal A et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 2013; 14: 86

[280] Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia. 2014; 34: 986–993

[281] Deutsches Register Klinischer Studien: Transkutane Vagusnervstimulation zur Therapie der chronischen Migräne https://drks-neu.uniklinik-frei-burg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00003681 2012;

[282] Chun Chieh Y, Wang HH, Chun Cho Y et al. High risk of gastrointestinal hemorrhage in patients with Epilepsy: A nationwide cohort study. Mayo Clin Proceedings 2013; 88: 1091–1098. doi:10.1016/j.mayocp.2013.06.024

[283] Camara-Lemarroy C, Escobedo-Zuniga N, Ortiz-Zacarias D et al. Prevalence and impact of irritable bowel syndrome in people with epilepsy. Epilepsy & Behavior 2016; 63: 29–33

[284] Bonaz B, Sinniger V et al. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol 2016; 594: 5781–5790. doi:10.1113/JP271539

[285] Yuan H, Silberstein S. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part II. Headache 2016; 56: 259–266. doi:10.1111/head.12650 Epub 2015 Sep 18

[286] Bonaz B, Picq C, Sinniger V, Mayolá JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. Neurogastroenterol Motil 2013; 25: 208–221

[287] Elger G, Hoppe C, Falkai P et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000; 42: 203–210

[288] Sackeim HA, Keilp JG, Rush AJ et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatmentresistant depression. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 53–62

[289] Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol 2010; 27: 130–138

[290] Sjögren MJC, Hellström PTO, Jonsson MAG et al. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. J Clin Psychiatry 2002; 63: 972–980

[291] Vonck K, Raedt R, Naulaerts J et al. Vagus nerve stimulation…25 years later! What do we know about the effects on cognition? Neurosci Biobehav Rev 2014; 45: 63–71

[292] Strzelczyk A, Willems LM. Gesundheitsökonomie. In: Schmitt F, Stefan H, Holtkamp M eds. Epileptische Anfälle und Epilepsien im Erwachsenenalter. Springer; Berlin, Heidelberg: 2020. doi:10.1007/978-3-662-59198-7_5

[293] Strzelczyk A et al. Cost of epilepsy: a systematic review. PharmacoEconomics 2008; 26: 463–476

[294] Strzelczyk A et al. Evaluation of health-care utilization among adult patients with epilepsy in Ger-many. Epilepsy Behav 2012; 23: 451–457

[295] Helmers SL et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011; 22: 370–375

[296] Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy – an update. Seizure 2008; 17: 387–388

[297] Benbadis SR et al. MRI of the brain is safe in patients implanted with the vagus nerve stimulator. Seizure 2001; 10: 512–515

[298] Fetzer S et al. A systematic review of magnetic resonance imaging in patients with an implanted vagus nerve stimulation system. Neuroradiology 2021; 63: 1407–1417

[299] Ding J, Wang L, Wang C, Gao C, Sun T. Is vagal-nerve stimulation safe during pregnancy? A mini review. Epilepsy Research 2021; 174: 106671

[300] https://vnstherapy.de/safety-information