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REVIEW

Vagus Nerve Stimulation (VNS) Therapy System in pharmacoresistant epilepsy: A literature review

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Epilepsy affects approximately 50 million of people worldwide and 30% of them are resistant to drugs. Neuromodulation is becoming a key option in patients with drug-resistant epilepsy who are not feasible for resective surgery. Vagus nerve stimulation (VNS) is the most commonly used adjunctive neuromodulatory method in every patient aged 4 years and older who is unsuitable for resective surgery. It is a minimally invasive, non-teratogenic, extracranial pacemaker-like device which delivers electrical stimuli to the vagus nerve and desynchronize aberrant cerebral rhythms involved in epileptogenesis. In this review we approached the information and clinical data of VNS development history, clinical applications and possible mechanism of action. We will also review optimal stimulation parameters and information about closed and open loop devices. Vagus nerve stimulation is safe, efficient with no significant side effects and substantial cost-saving benefit, that also shows an important improvement in mood, behavior, cognition and quality of life. The overall responder rate was observed in more than 50% of patients. On the other hand, it is not clear which patients will respond to this method of treatment and why the response is not immediate, there are no available biomarkers or other features like age, sex, seizure type/epileptic syndrome to predict response to vagus nerve stimulation therapy. The VNS Therapy System continues to be an important prospect in the treatment of pharmacoresistant epilepsy, that requires further studies in order to ensure the most advantageous therapeutic response.

Keywords: vagus nerve stimulation, epilepsy, refractory, neuromodulation

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Introduction

About 50 million of people worldwide suffer from epilepsy and approximately 30% of them are resistant to drugs[1]. Failure of achieving seizure freedom with two or more well tolerated, first line antiepileptic drugs (as monotherapies or combination) within 1-2 years from the treatment onset is defined as pharmacoresistant or intractable epilepsy [1,2]. Patients from refractory epilepsy group may be considered perfect candidates for resective surgery, which represents the most commonly used and studied surgical option. Resections may involve cerebral structures like medial temporal lobe, amigdalo-hypocampal complex or neocortex, in some cases selective multiple cerebral lobes resections, callosotomy or hemispherectomy may be performed [3-5].

Despite this wide spectrum of surgical methods, a lot of patients may continue to experience seizures. Studies have shown that approximately 30-40% of patients with temporal lobe epilepsy resections and 54-63% with extratemporal resections do not have adequate seizure control [6]. Neuromodulation is becoming a key option in every patient with intractable epilepsy who is not feasible for surgery [7,8]. FDA approved three main types of neuromodulatory approaches: vagus nerve stimulation VNS (1997), responsive neurostimulation RNS (2013) and deep brain stimulation DBS (2018).

The VNS Therapy System is the most commonly used adjunctive therapy approved for the management of drug-resistant epilepsy in patients aged 4 years and older for which surgery cannot be performed, has failed or is not recommended [9]. Patients with impossibility of opening the skull, multifocal unresectable epilepsy, recurrent seizures after surgery, epilepsy of unknown cause, foci near the eloquent cortex or unclear epileptogenic focus, can be considered suitable candidates for vagus nerve stimulation [10]. (Table 1)

Definition and history of VNS development

VNS is a low-risk, minimally invasive extracranial pacemaker-like device, which delivers chronically, intermittent electrical stimuli to the left vagus nerve which in turn, stimulates epileptogenic networks and desynchronize aberrant cerebral rhythms [12]. The cost-effectiveness of this method is well established with an considerable decrease

Table 1 Available neuromodulation options for intractable epilepsy [11]

	Examples	Efficacy
Invasive palliative treatment for drug resistant epilepsy	Vagus nerve stimulation (VNS)	Moderate quality evidence for its effectiveness
	Responsive neuro-stimulation (RNS)	Moderate to low quality evidence
	Deep brain stimulation (DBS)	Moderate to low quality evidence
Noninvasive palliative treatment for drug resistant epilepsy	Transcranial direct current stimulation (tDCS)	Moderate to very low quality evidence
	Transcranial magnetic stimulation (TMS)	Insufficient data to support the efficacy of these modalities
	Transcutaneous vagus nerve stimulation (tVNS)	Insufficient data to support the efficacy of these modalities
	Trigeminal nerve stimulation (TNS)	Insufficient data to support the efficacy of these modalities

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in status epilepticus, emergency visits, hospitalization and intensive care unit costs [13].

The implementation of vagus nerve stimulation started in the 1880s, when American neurologist J. Corning developed an applied several ,,carotid fork-like" instruments to decrease heart rate and cerebral blood flow by mechanical compression of the carotid artery and electrical stimulation of the vagus nerve in patients with epilepsy. He thought that decreasing ,,cerebral hyperemia" would dramatically reduce seizures. Initially he noticed a reduction in seizures frequency and duration, but despite multiple experiments and initial benefits, Corning's treatments did not produce a consistent result and were abandoned [14].

In the 90's multiple animal experiments took place in the idea of elucidating the importance and mechanism of VNS, one of them was performed by Zabara and colleagues in 1985, who noticed an anticonvulsive effect of VNS in dogs with induced seizures [15]. In 1987 Cyberonics Inc (Houston, Texas, USA) had developed the first pacemaker like device for vagus nerve stimulation and in 1988 first implantation was performed by neurosurgeon William Bell and neurologist James Kiffin Penry in the United States. In 1997 vagus nerve stimulation received FDA approval for adjunctive treatment of drug-resistant epilepsy and in 2005 for drug-resistant depression [16]. Over the past 20 years, device has been admitted in more than 70 countries and more than 125 000 patients worldwide have already benefited from implantation [10].

General principles of the device and clinical applications

The vagus nerve stimulator is implanted under the left subcutaneous pectoral area and includes pulse generator, spiral bipolar wired lead wrapped around the nerve, handheld magnet and specialized programming software for adjusting parameters of stimulation [16]. The intervention lasts between one and two hours, is performed under general anesthesia by specialized epilepsy surgeons and the optimal parameters of stimulation will be set by the neurologist. In the experimental studies stimulation of the right vagal nerve produced greater degree of bradycardia (due to innervation of sinoatrial node) and this is why the implantation is executed on the left side [9,10]. The device cannot be used in patients undergoing diathermy, patients with cardiac conduction disorders or in those with bilateral cervical vagotomy. Also VNS is not recommended to patients with obstructive sleep apnea, dysautonomia or chronic obstructive pulmonary diseases [17]. Risk of congenital malformations and teratogenicity is low in patients with VNS [18].

In the past some authors considered brain MRI a relative contraindication to VNS but modern devices have shown a good tolerability to the investigation. Fetzer and co-authors indicate in a systematic review that patients with VNS can safely perform cranial MRI (1.5 T and 3 T) without significant side effects. In 3 T MRI it is important to follow all the steps, technical conditions and guidelines required by LivaNova [19]. Stimulator is turned on 2 weeks after the surgery allowing the recovery after the intervention and offering the possibility to differentiate between cardiac adverse effects due to stimulation and those secondary to surgical manipulation [20]. The side effects of VNS can be classified as secondary to implantation (1,6% infections, 10% procedural pain, 1% vocal cord paralysis, 10% dysphonia) or to stimulation (10% oropharyngeal pain, 30% hoarseness, 10% dysphagia) [21-23]. Battery lasts up to 6-10 years (depending on the model and settings used), the battery lifespan decreasing with an increase in stimulation parameters. When battery reaches the end, the entire device is replaced to prevent opening of the hermetically sealed metal cased [24]. LivaNova recommend to deactivate and remove the device if there is not observed at least 50% seizure frequency reduction after 18 months of use but even so, other outcomes such as mood, cognition or quality of life improvements should be taken into consideration before removing the device [21].

Drug-resistant epilepsy is accompanied by depression, behavioral changes, anxiety, cognitive impairment and high risk of suicide, which profoundly affect the patient's quality of life. Kim et al evaluated VNS effects (on depression, anxiety and suicide) on 25 patients who underwent implantation and observed (both in seizure responders and also in non-responders) an important reduction in suicidality, depressive symptoms and an improvement in the quality of life. This improvement increased gradually over time with a considerable result at 1-2 years follow-up [25].

It was initially assumed that vagal stimulation was expensive therapy, but long term cost-effectiveness evaluation studies based on admissions to the emergency department or intensive care unit and multiple antiepileptic drugs administrations, have shown substantial cost-saving benefits. A study of 138 implanted patients with drug-resistant epilepsy with a follow-up of 4 years showed an important decrease in the numbers of hospitalizations (70% decrease) and the duration of hospitalization (67% decrease), respectively emergency room visits (99% decrease) [26]. In the majority of studies, the overall responder rate (≥50% seizure reduction) was observed in more than 50% of patients, with an important improvement over time.

Possible antiepileptic mechanism of action

The precise neuro-biological mechanism of VNS effect is still unknown, although data from experimental studies have suggested that an important role is attributed to structures such as nucleus of tractus solitarius (NTS), locus coeruleus (LC) and dorsal raphe nucleus (DRN). The NTS represents an important relay center for the vagal afferent sensory fibers (80% of the nerve fibers) which in turn sends projections to locus coeruleus, dorsal raphe nucleus (DRN), limbic structures and forebrain. Locus coeruleus (an important source of norepinephrine in the brain) represents a key central anticonvulsive target that

sends projections to the hippocampus, which is frequently involved in the temporal lobe epilepsy. DRN is responsible for sending serotonergic projections to the amygdala, diencephalon and cerebral cortex. There is a vast amount of studies showing that releasing of norepinephrine and serotonin exert an important antiepileptic effect through desynchronization of brain rhythms involved in epileptogenesis. Thalamocortical network is considered a robust structure through which aberrant cerebral rhythms are desynchronized.

There are other several animal studies about mechanisms of vagus nerve stimulation:

a. Neuroinflamation: increasing GABA in CSF, inhibition of tumor necrosis factor releasing from macrophages, conversing of macrophage's phenotypes from pro-inflammatory to reparative.

b. Neuroplasticity: reducing seizures occurence by elevation of brain derived neurotrophic factor.

c. Neuroexcitation: activation of muscarinic receptors and glutamate modulation with increase in cerebral inhibition [27-31].

d. Cerebral blood flow changes: Bohning et al (2001) and Lomarev et al (2002), in their functional MRI studies of depressed patients who recieved VNS therapy, have reported an increase in blood oxygenation level in the orbito-frontal cortex, temporal, parietal and occipital lobes, amygdala and hypothalamus [32]. Henry and colleagues measured blood flow through PET-CT in 10 patients who received VNS and found blood flow increasing in the medulla, thalamus, hypothalamus, right postcentral gyrus, insular cortex and decreasing in hyppocampus, amygdala and cingular cortex [33]. Kunii et al utilized near-infrared spectroscopy to evaluate task-induced cerebral blood flow changes in 21 patients with VNS and observed that cerebral blood flow did not change with stimulation alone, but it increased when the vagus nerve stimulation was paired with specific cognitive tasks [34]. Zhu et all performed a radiological study to evaluate the gray and white matter density changes after three months of VNS in 15 patients with DRE. The authors observed no significant modification at the level of subcortical nuclei but an increase of density in the left middle occipital gyrus, left cerebellum, left inferior parietal lobule and left gyrus rectus. The important reduction of density was observed in the left thalamus, left superior temporal gyrus, right inferior temporal gyrus and right cerebellum. Also changes of density were noticed in white matter tracts. Probably these microstructural changes are involved in the reduction of postoperative seizure frequency [35]. There are various imaging patterns, a high degree of clinical heterogeneity and no large conducted studies to draw an reliable conclusion at this point, but it can certainly be mentioned that vagus nerve stimulation influences cerebral blood flow and microstructure of gray and white matter.

Except the antiepileptic effect, vagus nerve stimulation also plays an considerable role in cognitive improvement through involvement of the anatomical structures which participate in memory formation and storage centers [31] and also in drug resistant depression through the serotonin and norephinephrine release with influencing on mood regulation pathways such as prefrontal cortex and limbic system [36].

Closed versus Open loop devices

Currently, open-loop (OL) and closed-loop (CL) modes are used. Open-loop models (Aspire 102, 102R, 103, 104, 105) are independent of brain activity and are not incorporated on stimulation protocols. These models consist of continuous on-off cycles accompanied by extra stimulation of a magnet which are applied by the patient or their caregivers to prevent, lessen or abolish seizures. Closed-loop have become available for about 5 years (most recently applied models AspireSR 106 and Sentiva 1000 used the AutoStim feature which is based on seizure detection algorithm (R-R intervals calculation) with triggering the autostimulation of the vagus nerve) [37]. The rising of heart rate occurs in 82% of ictal events, that's why CL VNS is a promising design. Cardiac-based seizures detection devices gained FDA approval in 2015 and offer solutions for patients with nocturnal seizures, cognitive impairment, physical disability or for patients who are unable to control the magnet [38]. Tzadok and colleagues analyzed an AspireSR 106 model in a group of 46 patients (ages 5-31 years) where 29 benefited from new implantation and 17 underwent replacement to the AspireSR model. At 13 ± 7.5 month follow-up there were 60.9% responders in the first implanted group and 59% in the replacement group [39]. Winston et al studied the effectiveness of OL and CL devices during the 2 year follow-up, in a group of 101 patients (31 CL and 70 OL) who met the criteria for stimulation, with a median age of 32 years. At 9 month follow-up was observed a reduction in frequency of seizures in about 75% of CL and 50% of OL group of recipients, but after 2 years there was no significant difference, with a 58% reduction of CL recipients and 55% of OL [40].

Optimal stimulation parameters

Optimal settings for VNS are not yet fixed, the most common parameters of stimulation recommended by manufacturers and researchers used in the present are: intensity 1.5-2.25 mA, pulse width 250-500 μs, frequency 20-30 Hz, *standard cycles:* 30 seconds on and 3-5 min off (highest responder rate) or *rapid cycles:* 7 seconds on and 30 seconds off. Also an important feature is magnet mode which comprise following parameters: intensity 0.25 mA, frequency 30 Hz, cycles of 30 seconds on and 5 min off. Usually the output current is increased with 0.25-0.5 mA every two weeks until reached target intensity. Polkey et al suggest that 30-60% of patients will never respond to treatment. More than that, if there is no response to 2 mA, a later response is doubtful [41]. The American Academy of Neurology established that the intensity of 1.5 mA and the fre-

quency of 250-300 μs can be favorable for tolerability and battery savings. Fahoum et al (in a comprehensive study of 1178 patients) suggested that the intensity of 1.625 mA and the pulse width of 250 μs had shown better outcome. They also observed that patients with shorter duration of the disease and higher duty cycles were identified to have greater response to VNS therapy [42]. Two blind, multicenter, randomized trials (EO3, EO5) compared low versus high-stimulation modes. At 12-week follow-up in the EO3 study was observed a 6.1% seizure reduction in low- and 24.5% in high-stimulation group, respectively in the EO5 study average seizures reduction were 15% and 28% [37,38]. Chambers and Bowen observed that high stimulation mode had significantly higher response for seizures reduction compared to low stimulation mode in adult patients [39]. Panebianco and co-authors in their systematic review of five randomized controlled trials with 439 participants, had shown that patients receiving high vagus nerve stimulation were 1.73 times more likely to have reduced seizures frequency compared to those receiving low stimulation [43].

As a result of these studies, guidance from professional societies conclude that rapid cycling mode was shown to be more effective and had higher response in seizure control than low-stimulation but with some theoretical risk of more adverse effects and battery depletion. All the parameters and dosing must be adjusted individually for each patient depending on tolerance and seizure outcome.

We have selected the studies with most statistically relevant results regarding the VNS therapy efficacy published since 2010 and summarized their bullet points in the table below *(Table 2)*.

Conclusion

Vagus nerve stimulation is the most commonly used, well-established, safe and efficient neuromodulatory approach that will maintain the leading place in the treatment of intractable epilepsy over the short and long term. This adjunctive therapeutic option does not interact with antiseizure medication, has no significant side effects and even if the adverse effects occurred, these tend to diminish in time. It was initially assumed that vagal stimulation was expensive therapy, but in long term evaluation, researchers observed a substantial cost-saving benefit. Closed-loop devices with AutoStim feature, based on ictal tachycardia detection set to rapid cycling mode, showed better results in seizures outcome. In the majority of studies, the overall responder rate (≥50% seizure reduction) was observed in more than 50% of patients, with an important improvement over time. The VNS was also approved by FDA in 2005 for the treatment of drug resistant depression, being demonstrated that patients who underwent implantation showed a considerably improvement in mood, behavior, cognition and quality of life, whether they are seizure responders or not. Events such as SUDEP (Sudden Unexpected Death in Epilepsy), status epilepticus, traumatic injuries were reduced in post stimulation period. On the other hand, it is not clear what is the exact mechanism of the VNS action, which patients will respond to this method of treatment and why the response is not immediate. Rarely a complete seizures freedom is obtained. The VNS may have an unfavorable impact on sleep apnea with a significant worsening in those with preexisting condition. There are no available biomarkers or other features like age, sex, seizure type/epileptic syndrome to predict response to

Table 2 Evidence of efficacy and studies results

Authors	Year	Average of age	Number of patients	Follow-up	>50% seizure reduction (%)	Bullet points
1. Elliot et al 2011	1997-2008	Mean age 11.1 years	141	5.2 years	50%	Similar response to stimulation in both: younger and older than 12 years groups, with no additional complications [44]
2. Englot et al 2011	1999-2011	<6 years 6-18 years >18 years	4483	1 year 2 years	56% 62%	Better response in patients older than 18 years, in those with focal seizures and in those with epilepsy duration of ten or more years [45]
3. Ching et al 2013	1995-2010	Mean age 35.80 years	100	1 year 2 years 3 years 8 years 10 years	26.21% 30.43% 48.10% 76.41% 82.90%	Demonstrates the long-term safety and efficacy of VNS in seizures reduction[46]
4. Arcand et al 2017	2010-2015	35.1± 13.3 years	30	1 year 2 years 3 years	48% 41% 50%	Patients required changes of dose (more often increase) or of the antiepileptic medication type in the majority of cases [47]
5. Kawai et al 2017	2010-2012	1-73 years	362	1 year 2 years 3 years	55.8% 57.7% 58.8%	There was an improvement in the quality of life at 12, 24 and 36 months after VNS implantation and the efficacy of therapy increased over time [48]
6. Flesler et al 2017	2001-2015	14.1 years	158	6.9 years	66.5%	Shows a better seizure control at 24 months of VNS [49]
7. Boluk et al 2022	2005-2020	29.5± 9.5 years	41	6 months 12 months 18 months	53.7% 68.3% 75.6%	Claim the effectiveness in controlling focal, generalized and combined type of epilepsy, with and important time-dependent effect[50]
8. Kostov et al 2022	1993-2021	Mean age 19.5 years	436	6.25 years	60%	Reveal that post-traumatic (68% median seizure reduction) and post-stroke epilepsy (75% median seizure reduction) and also patients with intellectual disability had better seizure outcome [51]

vagus nerve stimulation therapy. The VNS Therapy System continues to be an important prospect in the adjunctive treatment of drug-resistant epilepsy, which requires further studies in order to ensure the most advantageous therapeutic response.

Author's contribution

MV (Conceptualization, elaboration of the methodology and writing of the manuscript), RI (Editing, reviewing), PS (Investigation, reviewing), BR (Conceptualization, editing the original draft).

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. WHO. Epilepsy. 2022; https://www.who.int/en/news-room/fact-sheets/detail/epilepsy. Accessed August 1, 2022.
2. 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. Jun 2010;51(6):1069-1077 DOI: 10.1111/j.1528-1167.2009.02397.x.
3. Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. Nat Rev Neurol. Dec 2012;8(12):669-677 DOI: 10.1038/nrneurol.2012.181.
4. Spencer D, Burchiel K. Selective amygdalohippocampectomy. Epilepsy Res Treat. 2012;2012:382095 DOI: 10.1155/2012/382095.
5. Kim DW, Kim HK, Lee SK, Chu K, Chung CK. Extent of neocortical resection and surgical outcome of epilepsy: intracranial EEG analysis. Epilepsia. Jun 2010;51(6):1010-1017 DOI: 10.1111/j.1528-1167.2010.02567.x.
6. Englot DJ, Raygor KP, Molinaro AM, et al. Factors associated with failed focal neocortical epilepsy surgery. Neurosurgery. Dec 2014;75(6):648-645;discussion 655; quiz 656 DOI: 10.1227/NEU.0000000000000530.
7. Eastin TM, Lopez-Gonzalez MA. Stimulation and Neuromodulation in the Treatment of Epilepsy. Brain Sci. Dec 21 2017;8(1) DOI: 10.3390/brainsci8010002.
8. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. May 2005;128(Pt 5):1188-1198 DOI: 10.1093/brain/awh449.
9. Bigelow MD, Kouzani AZ. Neural stimulation systems for the control of refractory epilepsy: a review. J Neuroeng Rehabil. Oct 29 2019;16(1):126 DOI: 10.1186/s12984-019-0605-x.
10. Ma BB, Rao VR. Responsive neurostimulation: Candidates and considerations. Epilepsy Behav. Nov 2018;88:388-395 DOI: 10.1016/j.yebeh.2018.09.032.
11. Boon P, De Cock E, Mertens A, Trinka E. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Curr Opin Neurol. Apr 2018;31(2):198-210 DOI: 10.1097/WCO.0000000000000534.
12. Kim D, Kim T, Hwang Y, et al. Prediction of the Responsiveness to Vagus-Nerve Stimulation in Patients with Drug-Resistant Epilepsy via Directed-Transfer-Function Analysis of Their Perioperative Scalp EEGs. Journal of Clinical Medicine. 2022;11(13):3695 DOI: 10.3390/jcm11133695.
13. Ryvlin P, Jehi LE. Neuromodulation for Refractory Epilepsy. Epilepsy Curr. Jan-Feb 2022;22(1):11-17 DOI: 10.1177/15357597211065587.
14. Lanska DJ. J.L. Corning and vagal nerve stimulation for seizures in the 1880s. Neurology. Feb 12 2002;58(3):452-459 DOI: 10.1212/wnl.58.3.452.
15. Yang J, Phi JH. The Present and Future of Vagus Nerve Stimulation. J Korean Neurosurg Soc. May 2019;62(3):344-352 DOI: 10.3340/jkns.2019.0037.
16. Afra P, Adamolekun B, Aydemir S, Watson GDR. Evolution of the Vagus Nerve Stimulation (VNS) Therapy System Technology for Drug-Resistant Epilepsy. Front Med Technol. 2021;3:696543 DOI: 10.3389/fmedt.2021.696543.
17. LivaNova USA I. BRIEF SUMMARY OF SAFETY INFORMATION FOR THE VNS THERAPY®SYSTEM [EPILEPSY INDICATION]. 2021; https://www.livanova.com/epilepsy-vnstherapy/en-us/hcp/safety-information. Accessed August 15, 2022.
18. Suller Marti A, Mirsattari SM, Steven DA, et al. Experience on the use of Vagus Nerve Stimulation during pregnancy. Epilepsy Res. Oct 2019;156:106186 DOI: 10.1016/j.eplepsyres.2019.106186.
19. Fetzer S, Dibue M, Nagel AM, Trollmann R. A systematic review of magnetic resonance imaging in patients with an implanted vagus nerve stimulation system. Neuroradiology. Sep 2021;63(9):1407-1417 DOI: 10.1007/s00234-021-02705-y.
20. Thompson SL, O'Leary GH, 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;15:709436 DOI: 10.3389/fnins.2021.709436.
21. Cyberonics I. VNS Therapy System manuals. 2021; https://dynamic.cyberonics.com/manuals/index_iframe.asp. Accessed August 17, 2022.
22. Schulze-Bonhage A. Brain stimulation as a neuromodulatory epilepsy therapy. Seizure. Jan 2017;44:169-175 DOI: 10.1016/j.seizure.2016.10.026.
23. Fisher RS, Afra P, Macken M, et al. Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance--The U.S. E-37 Trial. Neuromodulation. Feb 2016;19(2):188-195 DOI: 10.1111/ner.12376.
24. Toffa DH, Touma L, El Meskine T, Bouthillier A, Nguyen DK. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. Seizure. Dec 2020;83:104-123 DOI: 10.1016/j.seizure.2020.09.027.
25. Kim JS, Kim DY, Jo HJ, et al. Effect of Long-Term Treatment with Vagus Nerve Stimulation on Mood and Quality of Life in Korean Patients with Drug-Resistant Epilepsy. J Clin Neurol. Jul 2021;17(3):385-392 DOI: 10.3988/jcn.2021.17.3.385.
26. Helmers SL, Griesemer DA, Dean JC, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less. Neurologist. May 2003;9(3):160-164 DOI: 10.1097/00127893-200305000-00004.
27. Mamounas LA, Altar CA, Blue ME, Kaplan DR, Tessarollo L, Lyons WE. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. J Neurosci. Jan 15 2000;20(2):771-782 DOI: 10.1523/JNEUROSCI.20-02-00771.2000.
28. Zagon A, Kemeny AA. Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve simulation therapy for refractory epilepsy? Epilepsia. Nov 2000;41(11):1382-1389 DOI: 10.1111/j.1528-1157.2000.tb00113.x.
29. 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. May 2011;117(3):461-469 DOI: 10.1111/j.1471-4159.2011.07214.x.
30. Navidhamidi M, Mehranfard N. Vagal nerve stimulation for refractory epilepsy: A brief review. Neuropsychiatry. 01/01 2016;6:149-160 DOI: 10.4172/Neuropsychiatry.1000134.
31. Broncel A, Bocian R, Klos-Wojtczak P, Kulbat-Warycha K, Konopacki J. Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. Brain Res Bull. Feb 2020;155:37-47 DOI: 10.1016/j.brainresbull.2019.11.011.
32. 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. Jul-Aug 2002;36(4):219-227 DOI: 10.1016/s0022-3956(02)00013-4.
33. Henry TR, Bakay RA, Pennell PB, Epstein CM, Votaw JR. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. prolonged effects at high and low levels of stimulation. Epilepsia. Sep 2004;45(9):1064-1070 DOI: 10.1111/j.0013-9580.2004.03104.x.
34. Kunii N, Koizumi T, Kawai K, Shimada S, Saito N. Vagus Nerve Stimulation Amplifies Task-Induced Cerebral Blood Flow Increase. Front Hum Neurosci. 2021;15:726087 DOI: 10.3389/fnhum.2021.726087.
35. Zhu J, Xu C, Zhang X, et al. Grey and white matter microstructure changes in epilepsy patients with vagus nerve stimulators. Clin Neurol Neurosurg. Oct 2021;209:106918 DOI: 10.1016/j.clineuro.2021.106918.
36. Lv H, Zhao YH, Chen JG, Wang DY, Chen H. Vagus Nerve Stimulation for Depression: A Systematic Review. Front Psychol. 2019;10:64 DOI: 10.3389/fpsyg.2019.00064.
37. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. Aug 2014;23(7):496-505 DOI: 10.1016/j.seizure.2014.02.012.
38. Tatum WOt, Helmers SL. Vagus nerve stimulation and magnet use: optimizing benefits. Epilepsy Behav. Jul 2009;15(3):299-302 DOI: 10.1016/j.yebeh.2009.04.002.

39. Tzadok M, Harush A, Nissenkorn A, Zauberman Y, Feldman Z, Ben-Zeev B. Clinical outcomes of closed-loop vagal nerve stimulation in patients with refractory epilepsy. Seizure. Oct 2019;71:140-144 DOI: 10.1016/j.seizure.2019.07.006.
40. Winston GM, Guadix S, Lavieri MT, et al. Closed-loop vagal nerve stimulation for intractable epilepsy: A single-center experience. Seizure. May 2021;88:95-101 DOI: 10.1016/j.seizure.2021.03.030.
41. Polkey CE, Nashef L, Queally C, Selway R, Valentin A. Long-term outcome of vagus nerve stimulation for drug-resistant epilepsy using continuous assessment, with a note on mortality. Seizure. 2022/03/01/2022;96:74-78 DOI: https://doi.org/10.1016/j.seizure.2022.01.017.
42. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in Epilepsy. Brain Stimul. May-Jun 2022;15(3):814-821 DOI: 10.1016/j.brs.2022.05.016.
43. Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev. Apr 3 2015(4):CD002896 DOI: 10.1002/14651858.CD002896.pub2.
44. Elliott RE, Rodgers SD, Bassani L, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr. May 2011;7(5):491-500 DOI: 10.3171/2011.2.PEDS10505.
45. Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. Neurosurg Clin N Am. Oct 2011;22(4):443-448, v DOI: 10.1016/j.nec.2011.07.002.
46. Ching J, Khan S, White P, et al. Long-term effectiveness and tolerability of vagal nerve stimulation in adults with intractable epilepsy: a retrospective analysis of 100 patients. Br J Neurosurg. Apr 2013;27(2):228-234 DOI: 10.3109/02688697.2012.732716.
47. Arcand J, Waterhouse K, Hernandez-Ronquillo L, Vitali A, Tellez-Zenteno JF. Efficacy of Vagal Nerve Stimulation for Drug-Resistant Epilepsy: Is it the Stimulation or Medication? Can J Neurol Sci. Sep 2017;44(5):532-537 DOI: 10.1017/cjn.2017.46.
48. Kawai K, Tanaka T, Baba H, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord. Sep 1 2017;19(3):327-338 DOI: 10.1684/epd.2017.0929.
49. Flesler S, Reyes G, Fortini S, et al. [Vagus nerve stimulation: treatment of 158 pediatric patients with a long-term follow-up]. Rev Neurol. Jun 1 2017;64(11):496-501.
50. Boluk C, Ozkara C, Isler C, Uzan M. Vagus Nerve Stimulation in Intractable Epilepsy. Turk Neurosurg. 2022;32(1):97-102 DOI: 10.5137/1019-5149.JTN.33775-21.2.
51. Kostov KH, Kostov H, Larsson PG, et al. Norwegian population-based study of long-term effects, safety, and predictors of response of vagus nerve stimulation treatment in drug-resistant epilepsy: The NORPulse study. Epilepsia. Feb 2022;63(2):414-425 DOI: 10.1111/epi.17152.