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Health Technology Assessment for Vagal Nerve Stimulation intervention

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SUMMARY

Epilepsy is one of the major neurological disorders and people with epilepsy are usually treated with Anti-Seizure Medication (ASM). ASMs are commonly used to prevent recurring epileptic seizures. However, ASM is ineffective for 30% of patients and they fail to achieve adequate response. They are known to have Drug Resistant Epilepsy (DRE). Vagal Nerve Stimulation (VNS) is one of the neuromodulations approaches recommended for people with DRE. A meta-analysis done by Englot et al, in 2011 reported that VNS is effective in reducing more than 50% of seizure frequencies. However, there is no consistent evidence of cost-effectiveness of VNS. There is a need to understand the cost effectiveness of implementing VNS for refractory Epilepsy in India. In this HTA study we are planning to study the (1) cost-effectiveness of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy in India. (2) Systematic review and meta-analysis to find the clinical efficacy of VNS; and (3) rapid review to understand the adaptation of VNS in India and other countries. For the first objective, the cost effectiveness of VNS as an adjunctive treatment to ASM for the treatment of refractory Epilepsy in India is studied. The costs of VNS treatment and ASM is taken from the published literature. In the base case, VNS+ASM had an estimated incremental cost effectiveness of ₹745798 compared to ASM alone. Sensitivity analysis was done to assess uncertainty in the model. The results of cost-effectiveness analysis has shown that VNS is a cost-effective treatment compared to ASMs alone. In line with the second objective, we have done a systematic review by systematically searching for clinical trials and observational studies that assessed the clinical efficacy of VNS in PubMed, Google scholar, Science direct, Cochrane library. We have selected the studies and collected the data following the Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA). The results of meta-analysis have shown that VNS is clinically effective with a pooled estimate of 48% of >50% seizure reduction collected from 23 studies. The rapid review was done for the third objective to understand the adaption of VNS in India. Though VNS yields high percentage of seizure reduction, it is not widely in use due to several factors including the cost and complexity of the treatment. These factors are briefly discussed in the rapid review. From the cost-effectiveness study, the systematic review and meta-analysis and rapid review conducted, it is evident that VNS is clinically effective and cost effective to treat drug resistant epileptic patients when compared to the treatment with ASMs alone.

1. INTRODUCTION

Globally, neurological disorders such as illnesses of the brain, spine, and nervous system, are the main cause of disability[1] and the second leading cause of death worldwide.[2] In the upcoming decades, the number of fatalities and disabilities brought on by neurological disorders will increase as this burden becomes more widely acknowledged as a global public health concern[2]. Globally, in 2016 the leading cause of DALY was neurological disorders and also the second leading cause of death.[3] Fifteen percent of the global burden of diseases is contributed by India and it was estimated that it will increase by 23% in 2025. In 2017, as per the Indian Council of Medical Research (ICMR), 18% of the total Years Lost to Disability (YLDs) are due to Mental and Neurological Disorders (MNDs).[4] Epilepsy is also one of the neurological disorders which contributes to high morbidity. Globally, 50 million people affected by epilepsy[5] in India, it was estimated that the overall prevalence of epilepsy is 5.59-10 per 1000 population.[6] Epilepsy patients who have seizures and do not respond to anti-epileptic drugs are considered to be drug-resistant epileptics (DRE). The condition has also been referred to as intractable, pharmaco resistant epilepsy. Anti-seizure medication (ASM) is the most common intervention for seizures in epilepsy. ASM usually starts as one drug and can progress to a combination of drugs.[7] The treatment of DRE is challenging and can be invasive and non-invasive. A review identified biomarkers of Vagus Nerve Stimulation (VNS) responsiveness in patients with drug resistant epilepsy.[8] Recent advances like a machine learning algorithm which is a predictive model to identify response to VNS was developed. The predictive model may enable better prediction of patients who are likely to benefit from VNS and assist with clinical decision-making.

About 50 million people worldwide are suffering from epilepsy. There about 10million persons with epilepsy (PWE) in India. Epilepsy is a condition that has been found to be associated with large treatment gap. Poverty and poor health infrastructure has been found to be contributory to this large treatment gap.[9] People with epilepsy can suffer from frequent and recurring seizures, varying in nature and severity. There is a wide range of potential impacts both on the equality of life of patients and their caregivers as well as the amount of health care resources required to manage the condition in both epilepsy patients and health systems. The

goal of epilepsy management is to reduce the frequency of seizures, and anti-seizure medications (ASMs) are the most common therapeutic intervention ASM treatment usually starts as monotherapy and may progress to a combination of drugs if needed. Approximately a third of people with epilepsy fail to achieve an adequate response to treatment with ASMs and can be describes a having drug-resistant epilepsy (DRE). Prevalence of DRE varies according to region and the definition of drug-resistance.

Various invasive methods are suggested like hemispherectomy, temporal lobectomy, and corpus colostomy for epileptic patients. However, these methods are highly invasive and are associated with surgical complications and postoperative deficits.[10] VNS is one of the neuromodulation treatments for DRE and International clinical bodies suggested VNS as effective for patients where surgeries and pharmacotherapy are not advisable. Neuromodulation includes deep brain stimulation, vagal nerve stimulation, intracranial cortical stimulation transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation.[11] Randomised controlled trials on VNS was first conducted on 1994 on 67 refractory partial seizure epileptic patients which showed an obvious reduction in the frequency of seizures. Later, in 1997, VNS was approved by the US Food and Drug administration (FDA) which implanted in the left cervical VNS device to treat refractory epilepsy. In 2010, non-invasive transauricular VNS (i.e nVNS) device was approved by Europe for the treatment of epilepsy, depression and pain in 2012.[12]

VNS is effective in reducing the frequency of seizures by ≥50%.[13] The treatment of epilepsy is a challenging task while selecting an appropriate drug or a combination of drugs that controls seizures most effectively at an acceptable level of adverse effects. Treatment of seizure disorder is almost always multimodal which includes suppression of recurrent seizures by prophylactic therapy with antiepileptic medications. Once the treatment of epilepsy is initiated, antiepileptic drugs are typically continued for at least two years. Tapering and discontinuing of antiepileptic drugs should be considered, if the patient has been seizure free for at least two years. Complete control of seizures in nearly 50% of patients is seen with an adherence to single drug treatment. In India, the management of neurological disorders by VNS is not widespread. There is a need to study treatment gap, efficacy and cost-effectiveness.

Objectives

- To estimate the clinical efficacy of VNS as treatment to reduce the frequency of seizures in refractory epilepsy patients through systematic review and meta-analysis
- To study the cost-effectiveness of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy in India
- To understand the level of adaption of VNS as a treatment practice refractory epilepsy patients in India and other countries

2. METHODOLOGY

Study Phases

This study has three phases (1) systematic review and meta-analysis to find the clinical efficacy of VNS; (2) cost-effectiveness of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy in India; and (3) To understand the adaptation of VNS in different countries.

(1) Systematic review and meta-analysis to find the clinical efficacy of VNS

This systematic review was conducted in updating the systematic review done up to 2007 and published by Dario J Englot et al, 2011. In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). In this study, we reviewed the clinical efficacy of VNS in terms of the reduction of seizure frequencies. This study is conducted based on the published literature from the previously conducted studies.

Screening and study selection

Clinical trials of VNS reporting the percentage of seizure reduction as the outcome were systematically searched in the databases like PubMed, Science direct, Google scholar, Cochrane library. The PIOS (P-Population, I-Intervention, O-Outcome, and S- Study design) approach was carried out to conduct the systematic review. The population considered were patients with drug resistant epilepsy who were implanted VNS, Intervention is VNS, and the outcome considered is Seizure reduction. The study design included was the clinical trials. The details of the search strategy are provided in the search strategy table. In compliant with the objective, the studies which measured the seizure frequency reduction through VNS in drug resistant epileptic patients were included. Studies that involved other VNS like transcutaneous

VNS are excluded. Also, Letter to editors, conference abstracts, reviews, pre-clinical studies were excluded from the study. After removal of the duplicate studies, the title and abstracts were screened and 23 articles are finally included for the final meta-analysis.

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. Zotero was used as a reference manager for this systematic review. The screening process was done using Rayyan software and analysed by R software.

PICO of the review

Population (P) : Drug Resistant Epileptic Patients

Intervention (I) : VNS+ASM

Comparator (C) : ASM

Outcome (O) : Seizure Frequency

Search strategy

We have used the following phrases as search terms, a detailed search strategy tabulated in Table-1. Vagal Nerve Stimulation, neurological disorder, neuromodulation, epilepsy, seizure, vagus nerve system, Vagus nerve stimulation, neurological disorder and clinical trial were the key terms used in the search.

Eligibility criteria

This review included the analytical studies that implanted VNS on clinical applications when used as an adjunctive treatment for patients with drug resistant epilepsy. Journal articles published in English between 1998 to 2022 period was included

Inclusion and Exclusion criteria

The studies which considered VNS as an adjunctive treatment for patients with drug resistant epilepsy among adults are included in this study. In this study, we have excluded the studies that considered children as the population and articles that are published in other language except English are excluded. Studies that involved other type of VNS like transcutaneous VNS are also excluded

Study selection

Abstract, title, and full-text reviews were performed by two independent reviewers. Disagreements were resolved by consensus or by a third reviewer. We screened the titles,

abstracts, and full text of the studies to confirm inclusion or exclusion. Studies with insufficient information to determine the use of VNS were excluded. We then incorporated the process of including and excluding studies in the final systematic review. This process was summarized in a PRISMA flowchart.

Data collection

From the selected articles, the necessary details were collected in a data extraction form prepared in Microsoft excel. The data extraction form captured the study design, sample size, seizure type, the duration of follow-up in months, mean or median percentage of seizure reduction, percentage of patients who had >50% seizure reduction, country where the study is conducted and the year of publication.

Data analysis

Based on the information collected, we estimated the standard error to find the confidence interval in order to do the meta-analysis. The heterogeneity of the studies was assessed using the I^2 statistic and presented through a forest plot. Cochran's Q test was employed, which calculates the weighted sum of squared differences between individual study effects and the pooled effect across studies. Q follows a chi-square distribution with k-1 degrees of freedom, where k represents the number of studies. Heterogeneity is considered to be present when the p-value obtained from the Q test is less than 0.1.

(2) Cost-effectiveness analysis of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy in India

In this phase, we have estimated cost-effectiveness based on economic valuation of VNS as an adjunctive treatment to anti-seizure medications for the treatment of drug resistant epilepsy done for England. This analysis done using hybrid modeling which involves decision tree and Markov modelling from the health perspective. We focused on assessing the impact of treatment for drug resistant epileptic patients through VNS procedure in comparison to ASM in the public health facilities in India.

(3) Rapid review to understand the adaptation of VNS

This review were include the literature that implanted VNS among adults who are drug resistant epilepsy patients. Information on how common VNS in India, what is the cost of the equipment,

cost of implanting, various therapies for seizures (surgical, pharmacotherapy, exercise, yoga), alternative therapies, the adaptation of VNS in India was discussed with experts. Overall we described the overview of current evidence of VNS on clinical applications when used as an adjunctive treatment for patients with drug resistant epilepsy.

3. RESULTS

(1) Systematic review and meta-analysis to find the clinical efficacy of VNS

Search Results

The electronic search retrieved 1023 articles. After applying filters, the final number of articles that we have got is 549 in the systematic review. In google scholar the search terms used were VNS, neuromodulation, and neurological disorder. The number of articles that were taken from google scholar are 9170. In Cochrane library the search term used was epilepsy and we obtained 9186 articles. After deletion of duplicates and screening the title and abstract, the final number of articles taken into meta-analysis is 23.

Study selection

The PRISMA flowchart describes the study selection process (Figure-1). Overall, the electronic search from various data bases retrieved 1023 articles. After removing (62) duplicates , screening titles (298) and abstracts (568) articles were screened. Out of those 95 articles, due to unavailability of data, 74 articles were excluded. We have selected 23 through full text scrutiny for the final analysis.

Characteristics of the studies included. The general characteristics of the included studies are presented in Table-1. These articles were published between 1998 and 2022. It was observed that there is no clinical trial conduced for studying the efficacy of VNS in India for the adult population with drug resistant epilepsy. Majority of the studies were conducted in USA (11). Of the 23 studies, 8 are RCTs conducted in USA, Germany and Belgium.

Figure 1: PRISMA Flow chart

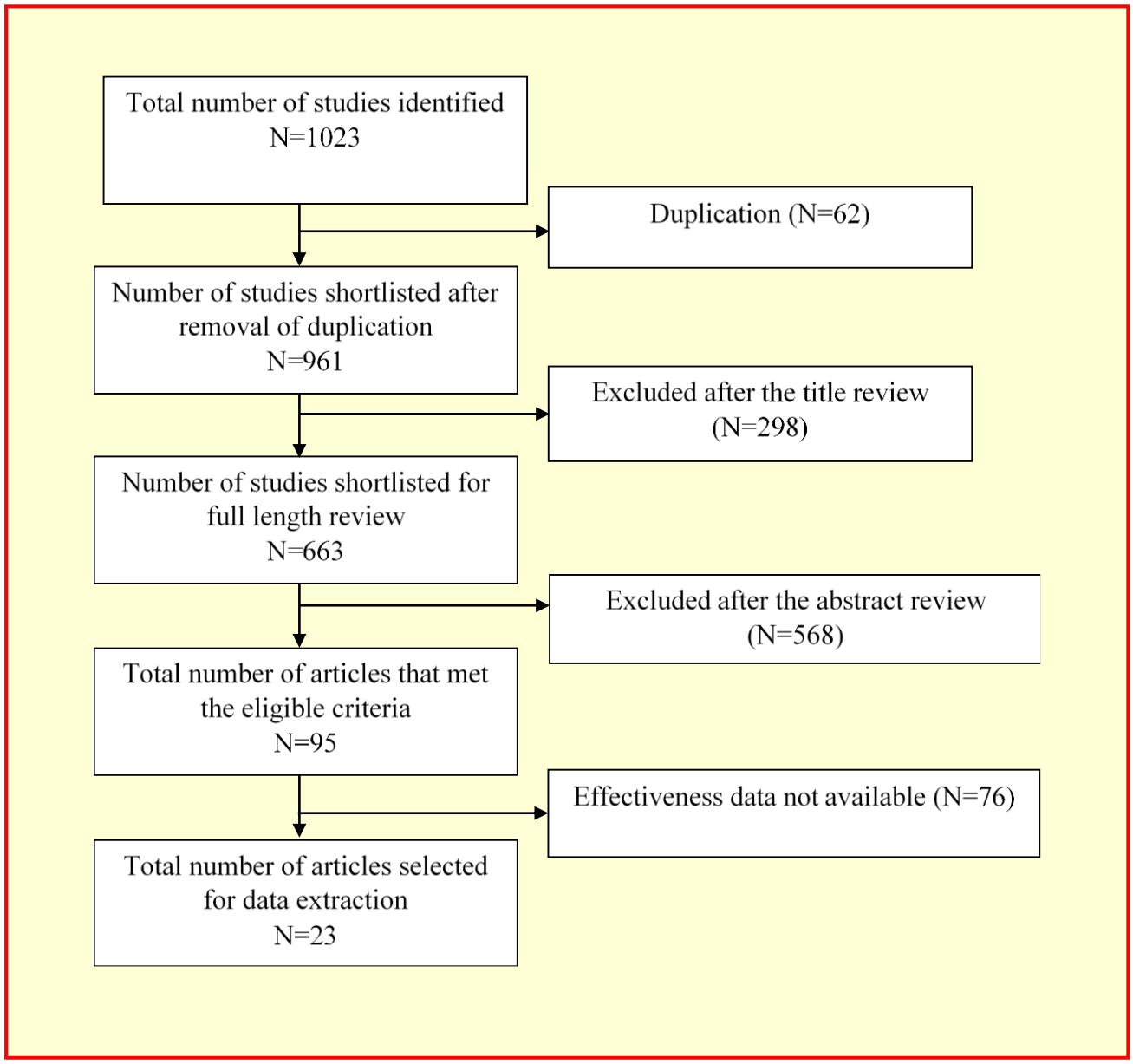


Table-1. Characteristics of the studies included in the review

S. No	Study	Year	Design	Sample	Seizure Type	Follow-up months	Centre	Seizure reduction (%)	Seizure reduction (>50%)	Country
1	Handforth et al[14]	1998	RCT	196	Partial	3	Multi	22	23	USA
2	Amar et al[15]	1998	RCT	17	Partial	4	Single	39	57	USA
3	Schermann et al[16]	2001	RCT	28	Mixed	NR	Single	30	45	Germany
4	DeGiorgio et al[17]	2005	RCT	61	Partial	3	Multi	26	29	USA
5	Ben-Menachem et al[18]	1999	Observational	64	Mixed	64	Single	NR	45	Sweden
6	Labar et al[19]	1999	Observational	24	General	3	Single	46	46	USA
7	DeGiorgio et al[20]	2000	RCT	195	Mixed	12	Multi	45	35	USA
8	Chavel et al[21]	2003	Observational	29	Partial	24	Single	53	54	USA
9	Vonck et al[22]	2004	RCT	118	Mixed	6	Multi	55	50	Belgium
10	Huf et al[23]	2005	Observational	40	NR	24	Single	26	28	USA
11	Ardesch et al[24]	2007	Observational	19	Partial	24	Single	25	33	Netherlands
12	Abubakr et al[25]	2008	Observational	31	Mixed	48	Single	52	20	USA
13	Boon et al[26]	1999	RCT	15	Partial	24	Single	11	54	Belgium
14	G L Morris[27]	2000	Observational	454	Mixed	36	Multi	43	37	USA
15	Elliott et al[28]	2009	Observational	19	mixed	115	Single	72	100	USA
16	Uthman et al[29]	2004	Observational	48	Partial	144	Single	52	60	USA
17	Santiago-Rodrı´guez[30]	2006	Observational	20	mixed	23	Single	56	80	Mexico
18	Wang et al [31]	2009	Observational	8	mixed	81	Multi	65	58	China
19	Muller et al [32]	2010	Observational	26	General	24	Single	NR	50	Hungary
20	Tzadok et al [33]	2019	Observational	51	General	13	Single	46	61	Israel
21	Herdt et al[34]	2007	Observational	138	General	12	Multi	51	59	Belgium
22	Ghaemi et al[35]	2010	Observational	144	General	28	Single	53	62	Germany
23	Hilderink et al[36]	2017	RCT	39	General	12	Single	NR	26	Netherlands

The electronic search retrieved 1023 articles. After removing duplicate articles, the total number of articles that were eligible for screening is 961. After doing the title and abstract review 95 articles were finally considered relevant to the objective. Due to the non-availability of data, 76 articles were excluded and 23 articles were finally included in the study. All the articles collected were from the year ranging from 1998 to 2022 (Table-2 & Figure-2). Out of the total 23 articles, 8 are Randomized controlled trials and 15 are observational studies (Figure-3). Across the 23 studies, the sample size varied from 8 to 454 with the average sample size of 78. The efficacy of VNS implantation of the drug resistant epileptic patients was measured in the percentage of patients who had >50% reduction in seizure. In RCTs the average percentage of patients who had the desired outcome is 39% and in the observational studies the average percentage is 53% (Figure-4). The average seizure reduction across the 23 studies through VNS implantation is found to be 43%. The majority of the studies were conducted in USA (11) followed by Belgium (3) (Figure-5). The seizure type had three classifications namely partial, mixed and general. Seven studies have discussed about the partial seizures, 9 about mixed seizures and 6 about the general seizures. There were 7 multi centric studies and 16 single centre studies out of total 23 studies. The duration of follow up of the patients ranged from 3 to 144 months.

Figure 2. Number of VNS efficacy studies included

Figure 3. Number of VNS efficacy studies by design

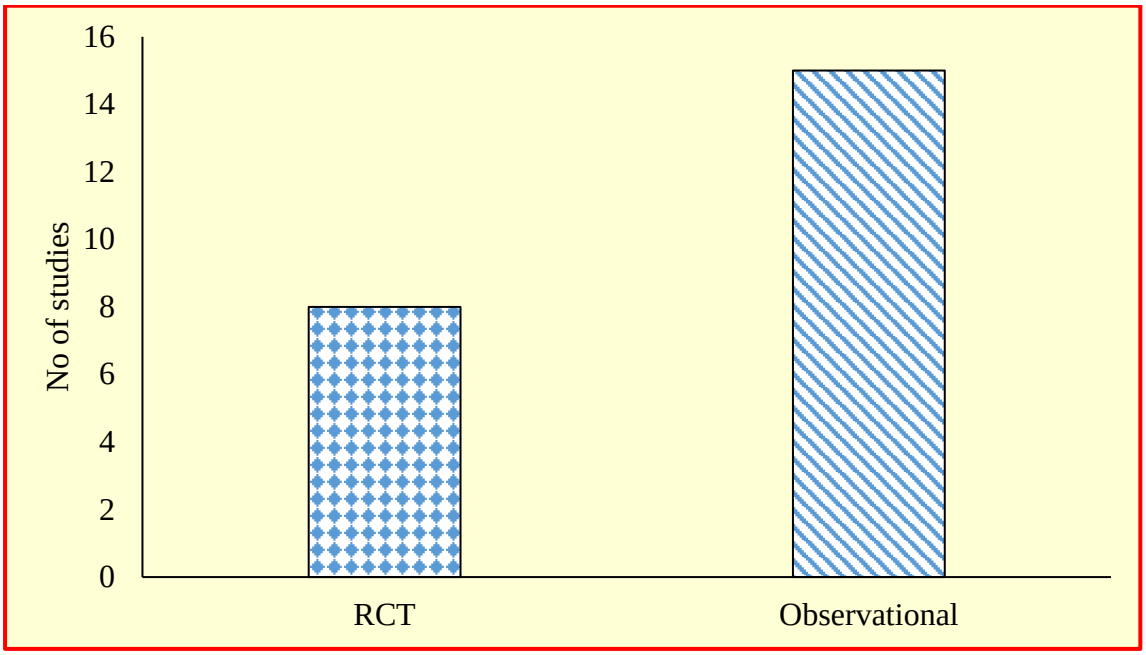


Figure 4. VNS efficacy rate in different studies

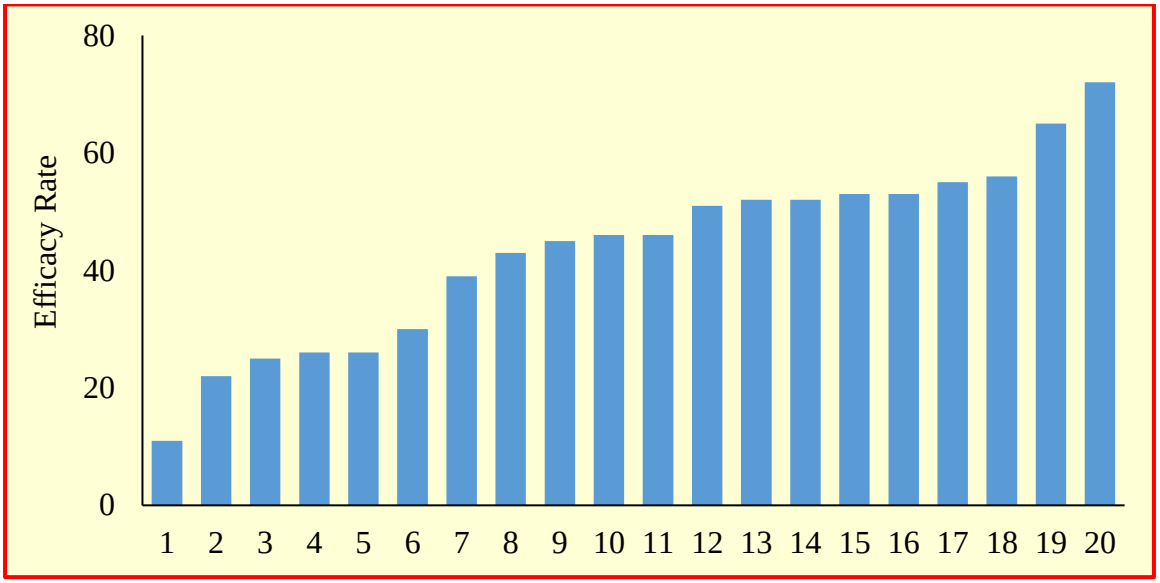


Figure 5. Number of VNS efficacy studies included

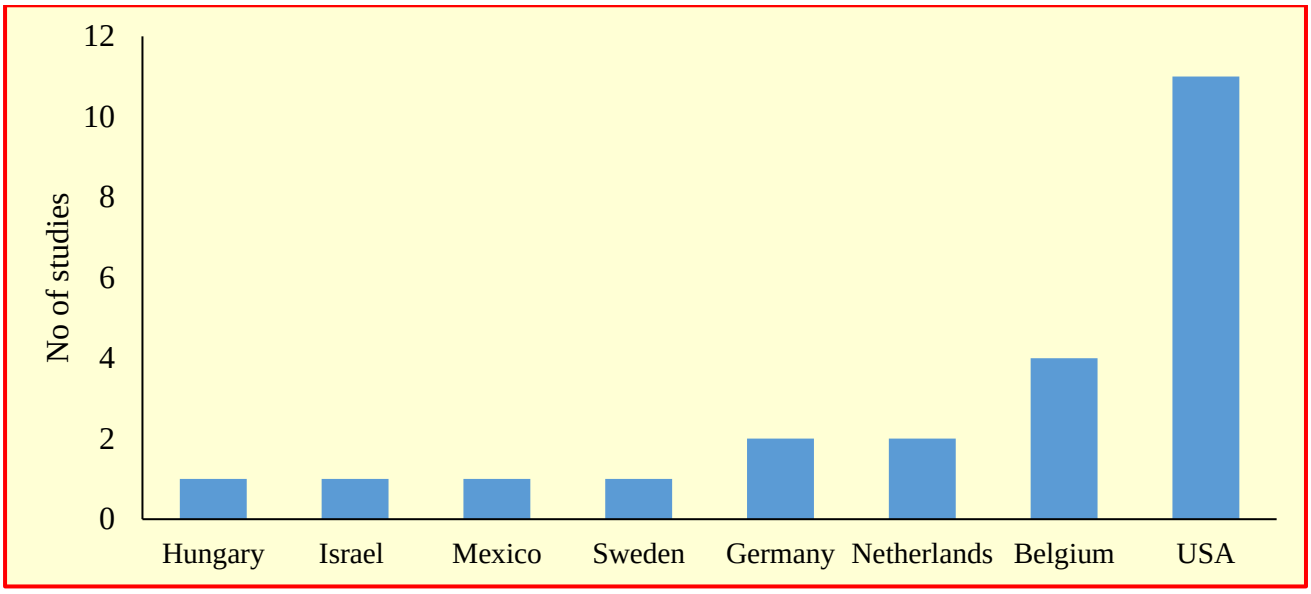
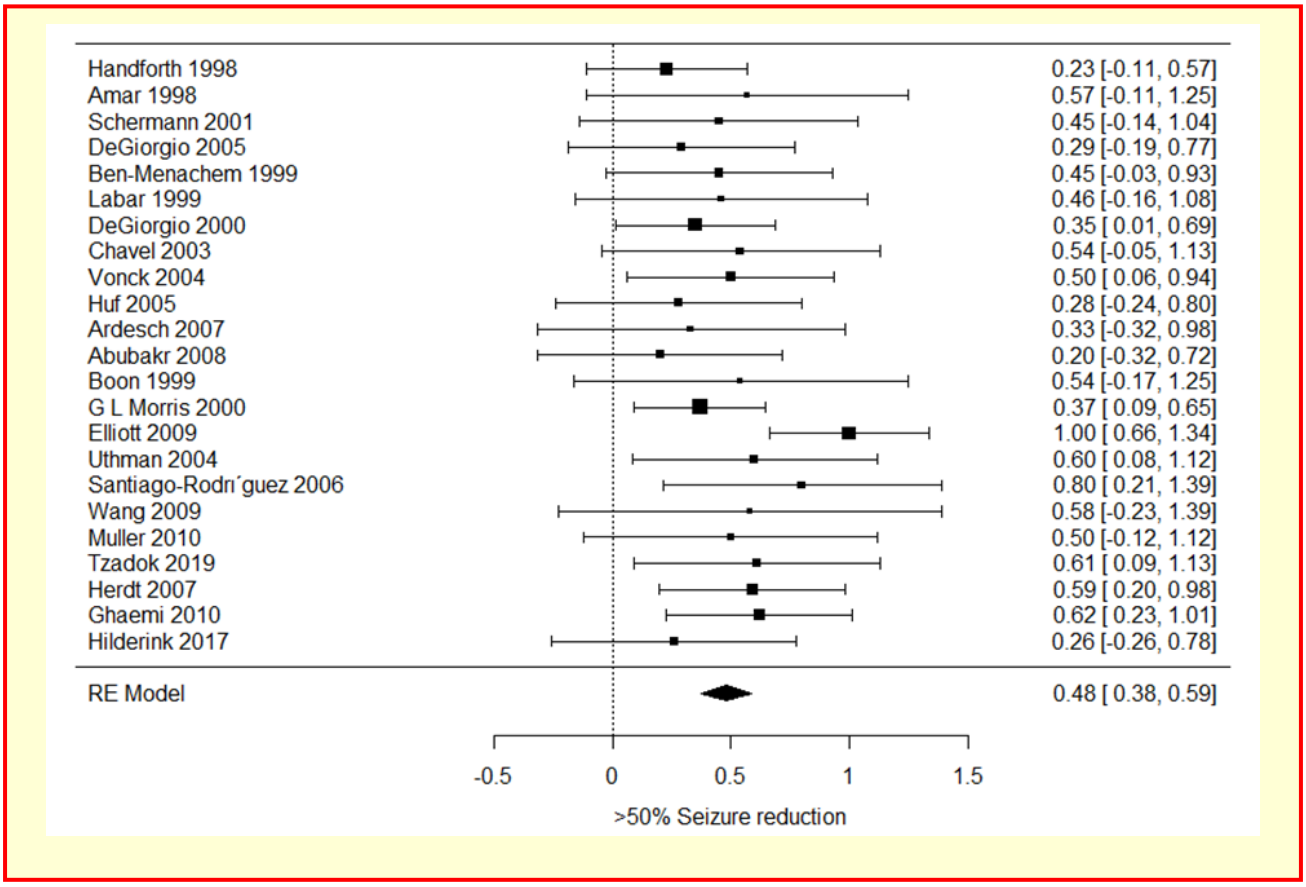


Figure 6. Forest plot depicting effect size in each study



The forest plot depicts the effect size of the VNS in all the studies along with the overall effect size. The vertical line indicates the null effect point. Confidence intervals were calculated using the standard error estimated with the 95% confidence interval. We analysed the effect of VNS on seizure reduction in drug resistant epilepsy patients across 1784 patients in the 23 reports. The overall >50% reduction is found to be 0.48 with the standard error 0.0538 and confidence interval ranging from 0.38 to 0.59. The randomized controlled trials data are included from 669 patients and observational studies data from 1115 patients. Across these 1784 patients, seizures were reduced by 48% ranging from 38% to 59% with the follow up months ranging from 3 to 144 months. The heterogeneity of the study is assessed using I^2 statistic, Cochrane test and visual presentation of forest plot. The I^2 statistic is found to be 12.18% which is found to be a very low heterogeneity and the Q statistic is found to be 18.0665 with the degrees of freedom being n-1 where n is the number of studies. Here the degrees of freedom is 22. The p value is 0.7020 which states that there is no heterogeneity among the studies and the pooled estimate is reliable. Our results suggest that around 50% of the patients who were treated with VNS benefits more than 50% of the reduction in seizure frequency.

We have also analysed the observational studies and RCTs separately and found the clinical effectiveness separately. The effectiveness of VNS in observational studies are found to be 0.55 ranging from 0.41 to 0.68 and the RCTs are found to be 0.36 ranging from 0.19 to 0.52.

(2) Cost-effectiveness analysis of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy

In terms of the cost effectiveness of Vagus Nerve Stimulation, there are several studies that has already been conducted in different countries. Few such studies are (1) an economic evaluation of VNS as an adjunctive treatment to anti-seizure medications for the treatment of drug resistant epilepsy by Raspin et al in England, (2) Health Technology Assessment report on Vagus Nerve Stimulation in Drug-Resistant Epilepsy by Marras et al in Italy, (3) Cost analysis of antiepileptic drugs available in India by Shukla et al, and (4) Direct medical costs of refractory epilepsy incurred by three different treatment modalities: A prospective treatment by Boon et al. We have summarized the findings of this study descriptively and given them from an Indian perspective as follows.

An economic evaluation has already been conducted in England for vagus nerve stimulation as an adjunctive treatment to anti-seizure medications for the treatment of drug-

resistant epilepsy in England. They have used a Cohort State Transition Model. That model simulates the costs and quality adjusted life years (QALYs) associated with two treatment strategies (1) VNS + ASMs and (2) ASMs alone. The model uses a 3-month cycle length and allows patients to transition between five health states based on their expected percentage reduction in seizure frequency. These percentage reductions are derived from data obtained from randomized controlled trials. This economic evaluation considers several cost components, including the costs of the VNS device, its installation, setup and removal, as well as costs associated with ASM therapy. Additionally, it accounts for costs related to adverse events associated with VNS (dyspnea, hoarseness and cough) and costs linked to epilepsy-related healthcare utilization, such as hospitalizations, emergency department visits, neurologist visits, and primary care visits. The study conducts various sensitivity analyses, including probabilistic sensitivity analysis, to explore the impact of uncertainty in the model's parameters and structure.

The cost-effectiveness of the VNS + ASMs strategy is found to be mainly driven by the relative reductions in expected seizure frequency and the resulting differences in healthcare resource utilization. Based on the economic evaluation, the study concludes that VNS is expected to be a cost-effective intervention for treating drug-resistant epilepsy in the England from health system perspective. This study have also showed that VNS will reduce the amount of anti-seizure medications (ASMs) to the patients. Similarly another study by Tatum et al., on economic evaluation of VNS showed that the reduction in the amount of ASMs consumed by the patient increases the cost-effectiveness of the VNS. This study have explored the different scenarios where patients undergo VNS could potentially reduce their ASM use, the analysis encompassed a range of costs associated with different ASM tried by the patients with drug resistant epilepsy. Alongside these varying costs, hypothetical percentage reductions in ASM use were considered. The findings have revealed that the cost-effectiveness of VNS has improved in these scenarios. The input parameters used for the study is given in Table-2.

Table 2. The input parameters used for cost-effectiveness analysis of VNS

	Input Parameters	Base Case Values
Unit costs (£) for health state care items	GP visits	£39
	A&E visits	£166
	Non-elective inpatient admission: epilepsy	£1,340
	Elective inpatient admission: epilepsy	£3,777
	Day case for epilepsy	£587
	Elective inpatient admission for epilepsy, incl. day cases	£1,022
	Neurologist appointment for adults	£186Adult
	Insertion of neurostimulator for treatment of neurological conditions for adults	£6,986
Summary of annual health care resource utilization (Frequency)	**100% seizure reduction (seizure free)**	
	Mean seizure frequency	0
	A & E visits	0
	Inpatient visits	0
	Inpatient non-elective	0
	Inpatient elective	0
	Outpatient neurologist visits	1.50 (1.28-1.73)
	GP visits	0.15 (0.11-0.20)
	75-99% seizure reduction	
	Mean seizure frequency	243
	A & E visits	1.35 (1.15-1.56)
	Inpatient visits	1.25 (1.06-1.44)
	Inpatient non-elective	1.04 (0.88-1.19)
	Inpatient elective	0.22 (0.18-0.25)
	Outpatient neurologist visits	7.45 (6.34-8.57)
	GP visits	2.58 (2.54-2.63)
	50-74% seizure reduction	
	Mean seizure frequency	287
	A & E visits	1.60 (1.36-1.84)
	Inpatient visits	1.48 (1.26-1.7)
	Inpatient non-elective	1.22 (1.04-1.41)
	Inpatient elective	0.26 (0.22-0.29)
	Outpatient neurologist visits	8.81 (7.49-10.13)
	GP visits	3.02 (2.98-3.07)
	<50% seizure reduction	
	Mean seizure frequency	506
	A & E visits	4.89 (3.53-6.46)
	Inpatient visits	6.12 (4.42-8.10)
	Inpatient non-elective	5.06 (3.66-6.70)
	Inpatient elective	1.06 (0.76-1.40)
	Outpatient neurologist visits	16.03 (11.58-21.19)
	GP visits	5.21 (5.17-5.26)
Annual costs per health state (£)	**100% seizure reduction (seizure free)**	
	A & E	£0

	Input Parameters	Base Case Values
	Inpatient	£0
	Outpatient	£279
	GP	£6
	75-99% seizure reduction	
	A&E	£225
	Inpatient	£1,609
	Outpatient	£1,387
	GP	£101
	50-74% seizure reduction	
	A & E	£266
	Inpatient	£1,902
	Outpatient	£1,639
	GP	£119
	<50% seizure reduction	
	A & E	£811
	Inpatient	£7,866
	Outpatient	£2,981
	GP	£205

Source: Raspin C, Shankar R, Barion F, Pollit V, Murphy J, Sawyer L, Danielson V. An economic evaluation of vagus nerve stimulation as an adjunctive treatment to anti-seizure medications for the treatment of drug-resistant epilepsy in England. J Med Econ. 2021 Jan-Dec;24(1):1037-1051.

In this study, the health state costs were taken from publicly available sources, in line with NICE health technology assessment methodology. General practitioner costs, Secondary care costs for hospital admissions, neurologist visits and VNS procedures are also included in this study. Costs for people with DRE were not available, and the costs for hospital admissions were sourced for people with nerve disorders, epilepsy or head injury, with the derived unit cost weighted for the associated activity by comorbidity score. In the sensitivity analysis, the cost of inpatient care is varied in line with the level of expected comorbidity. Anti-seizure medication costs and VNS treatment costs has been taken from published literature. Adverse event costs were taken and the mean cost per cycle is estimated and applied proportionally to the percentage of the cohort experiencing the event in any given three month cycle.

The study has shown that in the base case analysis, the use of VNS + ASMs is associated with an estimated ICER of £17,771 per QALY gained compared to using ASMs alone. That is, we have to spend £17,771 for gaining a QALY in VNS when compared to using ASMs alone.

The ICER represents the additional cost needed to gain one QALY by adding VNS to the treatment regimen.

We tried to measure the cost-effectiveness analysis of VNS adjunctive treatment to ASM for the treatment of refractory Epilepsy for India. Due to the unavailability of data in the Indian context, we have calculated ICER using the method given in this paper changing the available costs that we have taken from the available sources.

Table 3. Cost for various procedure involved in VNS in India

VNS	**Cost (₹)**
VNS procedure cost (cost of placement)	1,50, 000
VNS device cost – Demipulse	8,50, 000
VNS device cost – Aspire SR	10,50, 000
VNS device cost – Sentiva (newest model)	14,50, 000

Source: Siddharth Kharkar. Epilepsy Surgery Cost in India 2023. Neuro+ Epilepsy and Parkinsons Clinic. https://drkharkar.com/epilepsy-surgery-cost-in-india-best-epilepsy-treatment-in-india/

A budget impact study has been conducted by Purser MF et al., for USA in 2018 for assessing the expected budget Impact and Health Outcomes of Expanded Use of VNS Therapy for Drug-Resistant Epilepsy. In this study they have developed an excel model to compare the costs of AED treatment with the costs of VNS plus AED treatment. Costs included VNS device, placement, programming, and battery changes; adverse events associated with VNS (cough, voice alteration, device removal resulting from surgical site infection); AEDs; and seizure-related costs affected by seizure frequency, which affects resource utilization (i.e., hospitalizations, emergency department visits, neurologist visits). To estimate the potential savings with VNS due to a reduction in seizure frequency. The relative difference is found to be the maximum in 3rd to 5th year. The average relative difference between cost without VNS and cost with VNS is found to be 21.5%. In conclusion, this study has found that VNS is a proven intervention that offers a long-term solution for patients with DRE by reducing seizure frequency, which leads to lower resource utilization and lower costs.

Table 4. Budget impact for USA

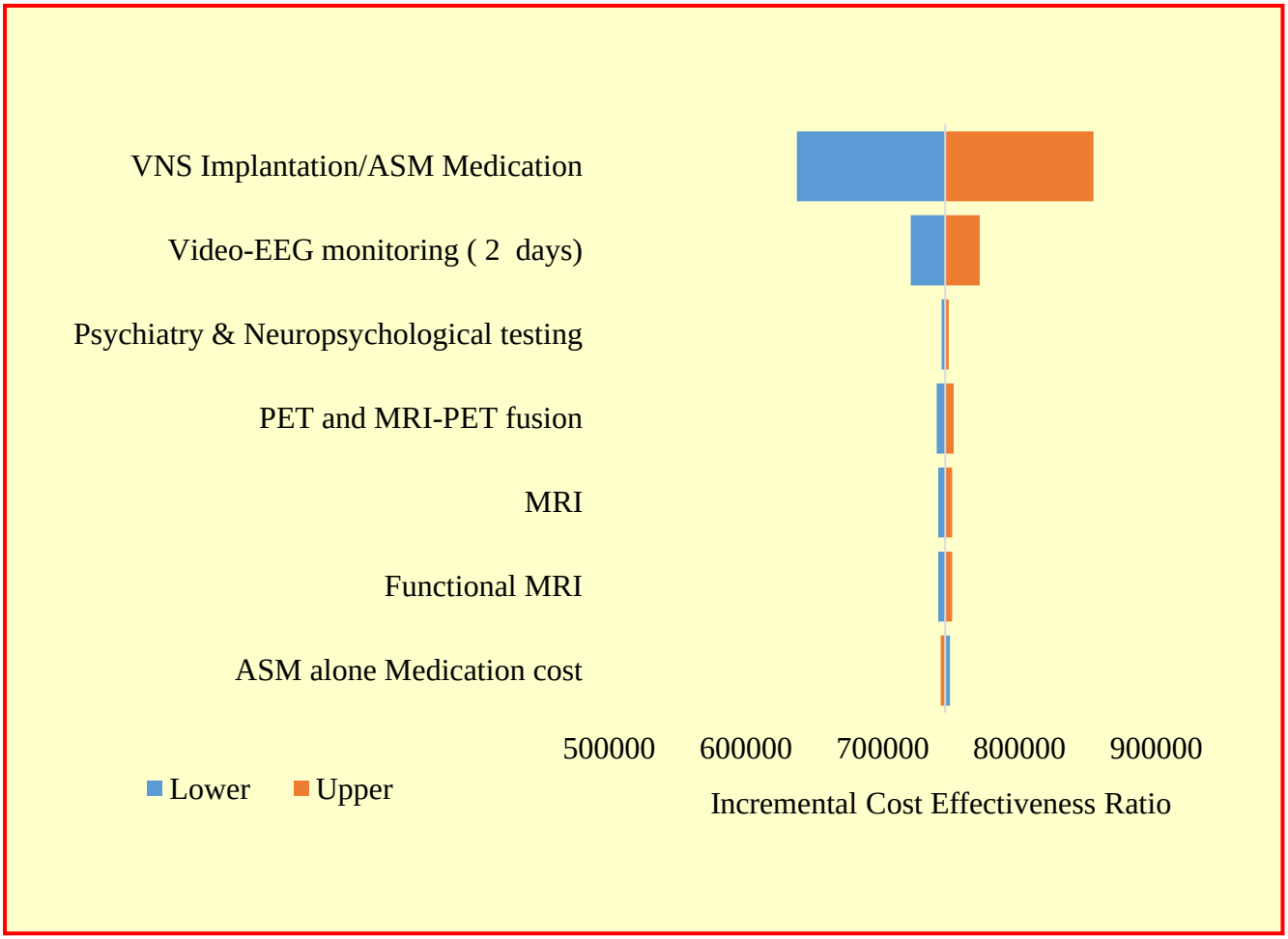
	1st year	2nd year	3rd-5th year	Total years
Cost without VNS	$110,709,545	$110,709,545	$110,709,545	$553,547,724
Cost with VNS	$141,644,874	$74,932,599	$72,657,493	$434,549,953
Budget impact	$30,935,329	($35,776,946)	$38,052,052	$118,997,771
Relative difference	27.94%	32.32%	34.37%	21.5%

Health Technology Assessment Report on Vagus Nerve Stimulation in Drug-Resistant Epilepsy review on International journal of Environmental Research and Public Health. This study assessed the clinical, organizational, financial, and economic impact of VNS therapy in drug-resistant epilepsies and established the congruity between costs incurred and health service reimbursement. VNS is a palliative treatment for reducing seizure frequency and intensity. Despite its economic cost, VNS should improve patients' quality of life and reduce family care needs. This HTA analysis focused mainly on the following issues: (a) social impact and costs of the disease; (b) clinical results after VNS therapy; (c) quality of life after VNS therapy; (d) economic impact and productivity regained after VNS; and (e) costs of VNS. A review with economic modelling has estimated the cost of epilepsy in 28 European countries. Despite a prevalence of 4.3 to 7.8 patients per 1000 persons, the total cost in Europe was estimated at EUR 15.5 billion, of which the indirect costs accounted for 55%, the direct costs of health (particularly outpatient care which entailed an expenditure of EUR 1.3 billion) accounted for 18%, and the non-medical cost for 27%; the cost per case treated/year ranged from EUR 2000 to 11,000. The economic burden of epilepsy is substantial, and it is inversely proportional to seizure control. Costs are higher in the first year after diagnosis than in the following years and varied according to the age of the patient. The major cost driver is hospitalization (63.7%), followed by drugs (10.5%), day-hospital visits (4.1%), outpatient visits (3.85%), other tests (3.1%), and electroencephalograms (2.3%). In particular, direct costs (outpatient and hospital) are based also on the age of onset of the disease, epilepsy features, frequency of seizures, and type of ASDs taken. In addition, indirect costs (for example: lost productivity) account for about half of the total costs. In addition to the economic cost the social burden, in terms of stigma and poor quality of life in patients of different ages, prognosis, comorbidity, and treatment response due to epilepsy is also considerable.

Table 5. Cost-effectiveness analysis for India

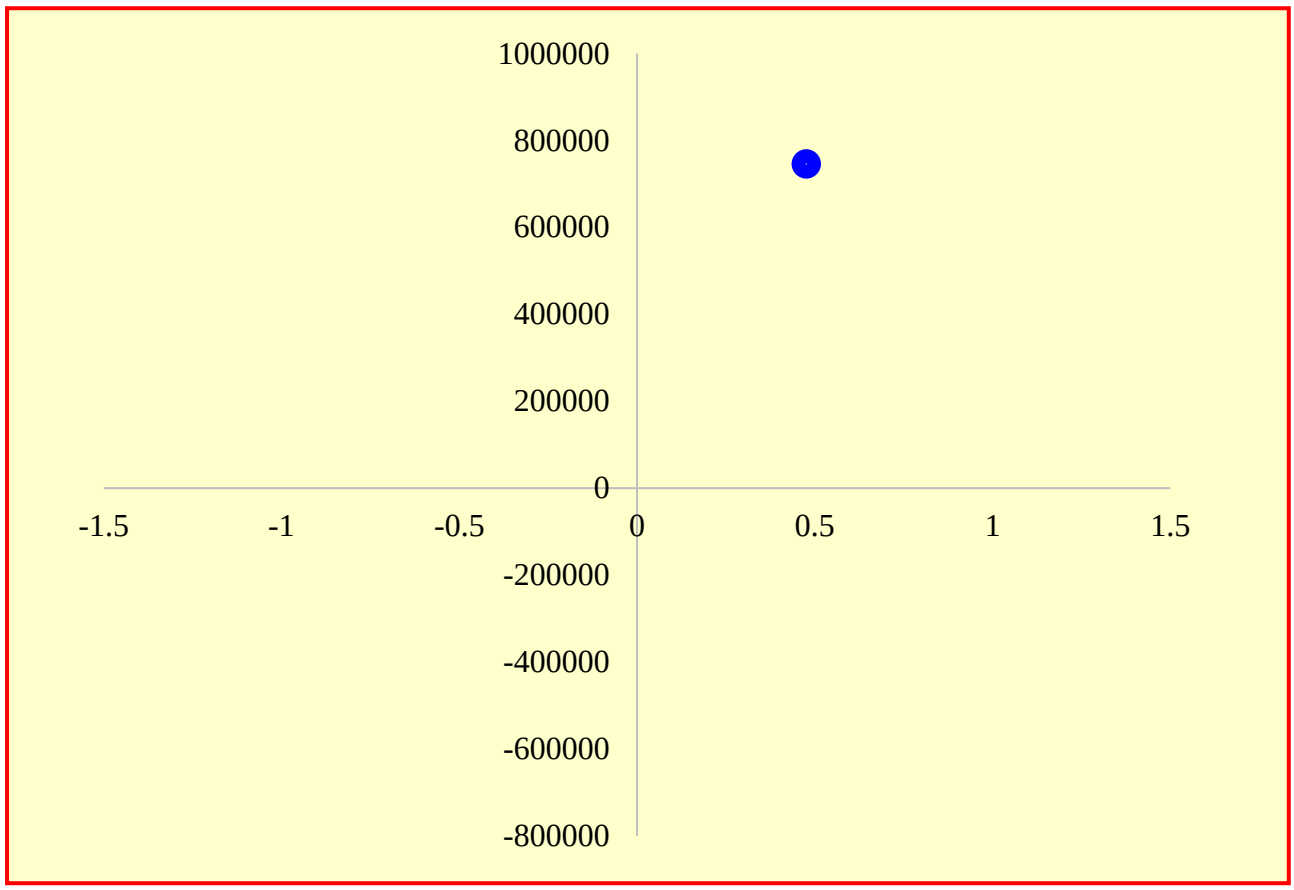
Cost	VNS + ASM (₹)	ASM alone (₹)	Increment
MRI	12,000	0	12,000
PET and MRI-PET	15,000	0	15,000
functional MRI (fMRI)	12,000	0	12,000
Video-EEG monitoring (2 days)	60,000	0	60,000
Psychiatry & Neuropsychological testing	6,000	0	6,000
VNS Implantation/ASM Medication	2,58,064	8064	2,50,000
Total costs	3,63,064	8,064	3,55,000
Health outcomes			
Life years	8.387	8.387	0
QALYs	6.118	5.642	0.476
Incremental outcomes			
ICER (cost per QALY)			745798.3

Figure 7. One Way Sensitivity Analysis



One Way Sensitivity analysis was done to assess the uncertainties around the model. The tornado diagram (Figure 7) depicts the parameters that highly influences the ICER value. The parameter cost of VNS implantation/ASM medication is found to be the parameter that is highly influencing the ICER value than the other parameters followed by Video-EEG monitoring for 2 days.

Figure 8. Cost effectiveness plane



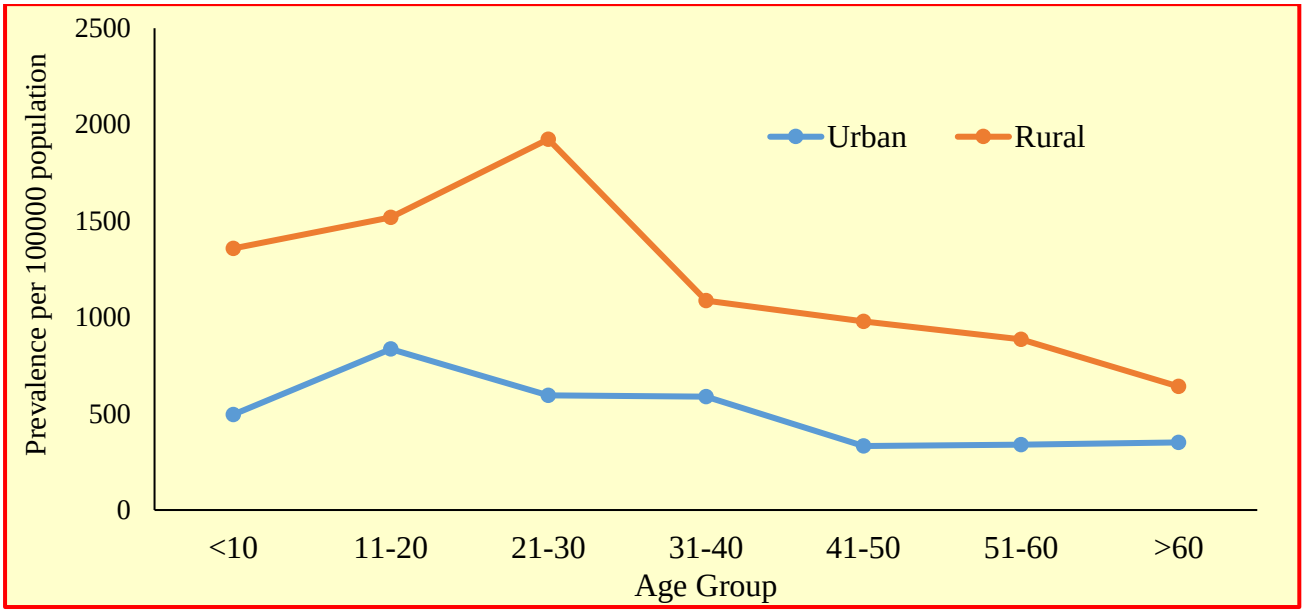
The cost-effectiveness plane shows that the ICER value for gaining a QALY through VNS+ASM treatment for DRE patients is ₹745,798. This value falls in the first quadrant, indicating that it is in the "More cost, more effective" region of the plane. In summary, this means that while VNS is a successful treatment that can reduce seizures which is required for only the small proportion of DRE patients, it is also expensive and not easily affordable. Therefore, VNS cannot be considered as the most cost-effective option for a broader population.

(3) Understanding the adaptation of VNS in India

Prevalence of Epilepsy in India

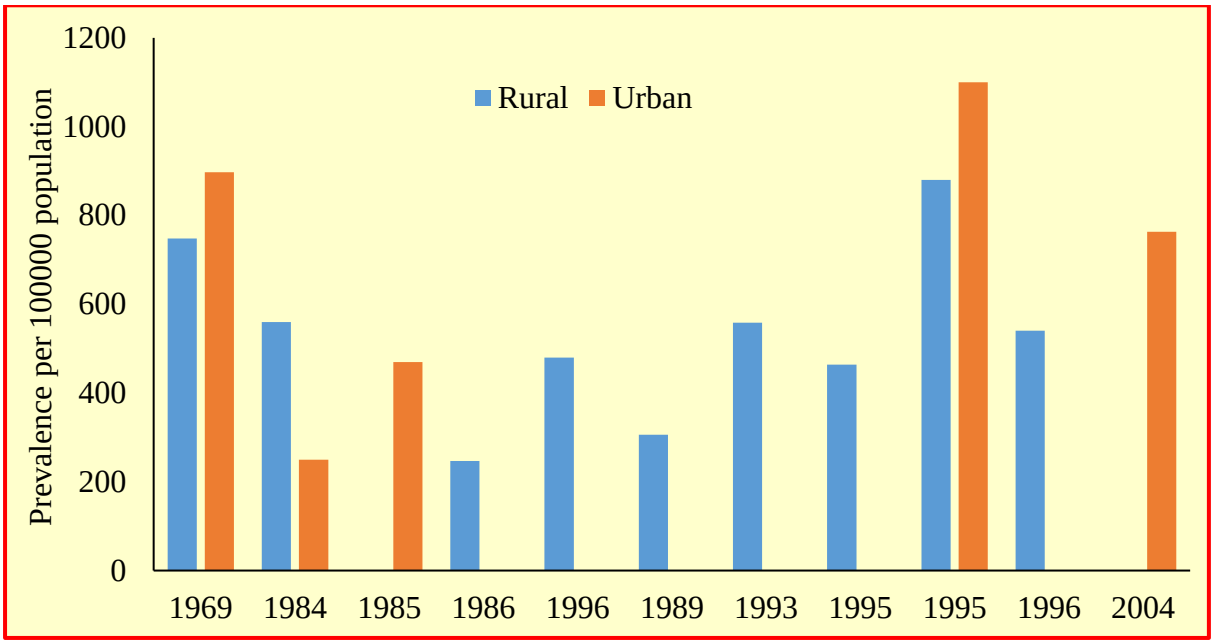
According to the WHO, of the 50 million people with epilepsy worldwide, 80% reside in developing countries. It was estimated that Epilepsy was account for 0.5% of the global burden of disease. It is estimated that there are more than 10 million person with epilepsy in India. Its prevalence is about 1% in India and the prevalence is higher in rural (1.9%) as compared to urban population (0.9%). The age adjusted prevalence ratio of active epilepsy is 4.7 per 1,000 population. This may be underestimated due to methodological differences in prevalence estimation. With respect to incidence of epilepsy, there are very few incidence studies from India. The age standardised incidence rates reported was 27.3 per 100,000 population per year. The exact magnitude of medically intractable epilepsy in India is unknown.

Figure 9. Age specific prevalence of Epilepsy in India



Source: Santhosh NS, Sinha S, Satishchandra P. Epilepsy: Indian perspective. Ann Indian Acad Neurol. 2014 Mar;17(Suppl 1):S3-S11.

Figure 10. Year wise prevalence of Epilepsy in India



Source: Santhosh NS, Sinha S, Satishchandra P. Epilepsy: Indian perspective. Ann Indian Acad Neurol. 2014 Mar;17(Suppl 1):S3-S11.

Treatment Gap

In India, with less than 2,000 neurologists and estimated 5 to 6 million patients with active epilepsy. There is huge need to strengthen epilepsy services. In many developing countries, people with epilepsy do not receive appropriate treatment for their condition, India is not exceptional. There is a treatment gap in accessing health care facilities for diagnosis and treatment, and also not adhering to the prescribed antiepileptic drugs. The gap is reported to be influenced by various factors including lack of access to health facilities, lack of knowledge of antiepileptic drugs, poverty, cultural believes, stigma, poor health delivery infrastructure and shortage of trained professionals. The magnitude of epilepsy treatment gap in India ranges from 22% in urban to 90% in village.

Epilepsy Treatment

Human brain is the coordinating centre of body and it the hub for most of the important neurological activities. These activities are coordinated with the help of electrical signals which are produced and received by brain with the help of neurons. It is when this electrical activity becomes uncoordinated **the condition is called as Epilepsy**. Most people with epilepsy treated with medications called antiepileptic drugs. But these medications may not work in some people or unable to tolerate the side effects. This may happen when the seizers are being

produced throughout brain or the medications are unable to control them. It was suggested that one third of epilepsy patents, the seizers are very difficult to control medication alone. This condition called drug resistant epilepsy (DRE). Another option of treatment is surgical intervention to remove the part of the brain that causes seizers. However, not every one of this candidate for surgery. VNS is an adjuvant treatment that has been approved by FDA for those suffer from focal (partial epilepsy and that are not responding to antiepileptic medications. About 20-30% of persons developing epilepsy continue to exhibit chronic recurrent seizures despite optimal treatment with AEDs. Nearly one-third of the patients with newly diagnosed epilepsy on long-term follow-up will have their seizures unsatisfactory controlled by treatment with available AEDs. Intractable epilepsy is defined as occurrence of two or more seizures per month for a period of more than 2 years despite using two or more AEDs. These patients also suffer from hard-to-treat depression (treatment resistant depression). It can be life threatening disease.

Cost of VNS therapy in India

There is a wide range of variation in the prices of drugs marketed in India. There is a wide variation in the prices of different brands of same antiepileptic agent in Indian market. It was reported that wider variation of different brands of the same oral antiepileptic drugs in India market is very wide. Treatment of epilepsy has a long course with compliance being a key factor for successful treatment. It was recommended that improved adherence to treatment can be ensured by decreasing the cost of therapy by changing the government policies and regulations and creating awareness among treating physicians for switching to cost-effective therapy. High medical costs should be a cause of concern for policy makers and service providers. It was noted that clinicians usually do not appreciate the difference between inexpensive and expensive drugs. The average percentage price variation of different brands of the same oral antiepileptic drugs in India market is very wide. Treatment of epilepsy has a long course with compliance being a key facts for successful treatment.In India market, there are large numbers of branded drugs available, variable pricing between the different brands of the same formulation is widely prevalent in Indian drug market. In India majority of the health costs have met by the out of pocket expenses by the patients. High medical costs should be a cause of concern for policy makers and service providers.

The cost of VNS in India can vary significantly based on several factors, including the specific medical facility, the type of VNS device used, the surgeon's fees, and other associated

medical expenses. Generally, the total cost of VNS in India can range from ₹1,50,000 to 15, 00,000 or more. This cost covers the various components (Table-5).

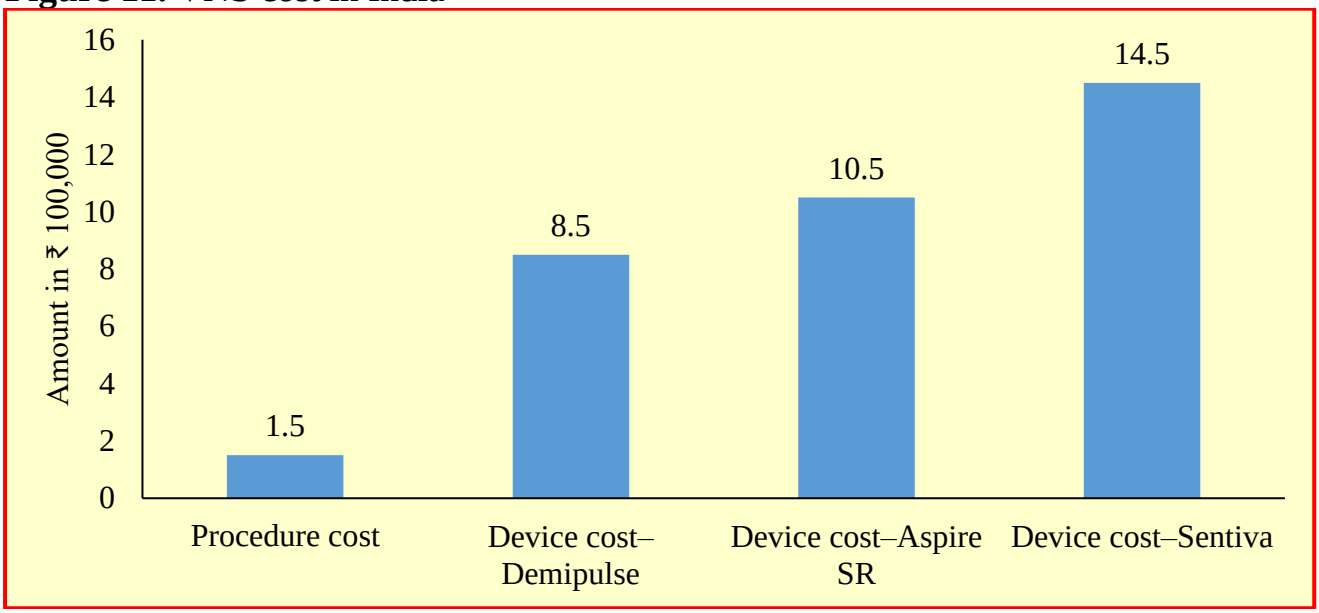
Table 6. Different components of VNS cost

Components	**Description**
VNS Device	The cost of the VNS device itself is a significant portion of the total expense. Advanced and newer models of VNS devices might be more expensive compared to older versions.
Surgical Procedure	The surgical implantation of the VNS device involves the expertise of a neurosurgeon and anesthesiologist. Their fees, along with the charges for the operation theater and other medical facilities, contribute to the overall cost.
Hospitalization and Follow-up	The cost also includes expenses related to the patient's hospital stay, post-operative care, and follow-up visits with the medical team.
Medication and Tests	Before and after the procedure, patients need certain tests and medications, which are additional costs to consider.
Insurance Coverage	Some health insurance plans in India provide coverage for VNS, partially or in full, depending on the policy terms and the condition being treated.
Geographic Location	The cost of medical procedures can also vary based on the region or city in India where the treatment is sought. Major metropolitan cities might have higher costs compared to smaller towns. It is essential for patients considering VNS as a treatment option to consult with a qualified neurologist or neurosurgeon to discuss the specifics of their case, understand the potential benefits and risks, and get a personalized estimate of the overall cost involved.

Table 7. Difference between Vagus Nerve Stimulation (VNS) and Anti-seizure Medications (ASM)

Components	VNS	ASM
Treatment Type	Surgical intervention involving device implantation	Medications taken orally or intravenously
Mechanism of Action	Electrical impulses stimulate the vagus nerve	Chemical substances act on the brain
Mode of Administration	Implanted device activated externally or programmed internally	Oral tablets, liquid, or injections
Treatment Application	Adjunctive therapy for drug-resistant epilepsy	Primary treatment for epilepsy
Treatment Response	Gradual and may take several months to show effects	Relatively fast; effects may be immediate or within days
Seizure Control Effectiveness	May reduce seizure frequency and severity	May provide significant seizure control
Side Effects	Mild to moderate; can include voice changes, throat discomfort, or cough	Can vary widely depending on the medication; may include dizziness, drowsiness, mood changes, etc.
Long-Term Use and Compliance	Implantation requires long-term commitment	Requires consistent adherence to medication schedule
Suitability for Patients	Typically considered for patients with drug-resistant epilepsy or limited medication effectiveness	Commonly prescribed for a wide range of epilepsy patients based on seizure type and other factors
Cost	Initial high cost for device implantation and follow-up	Generally more affordable in comparison to surgical intervention

Figure 11. VNS cost in India



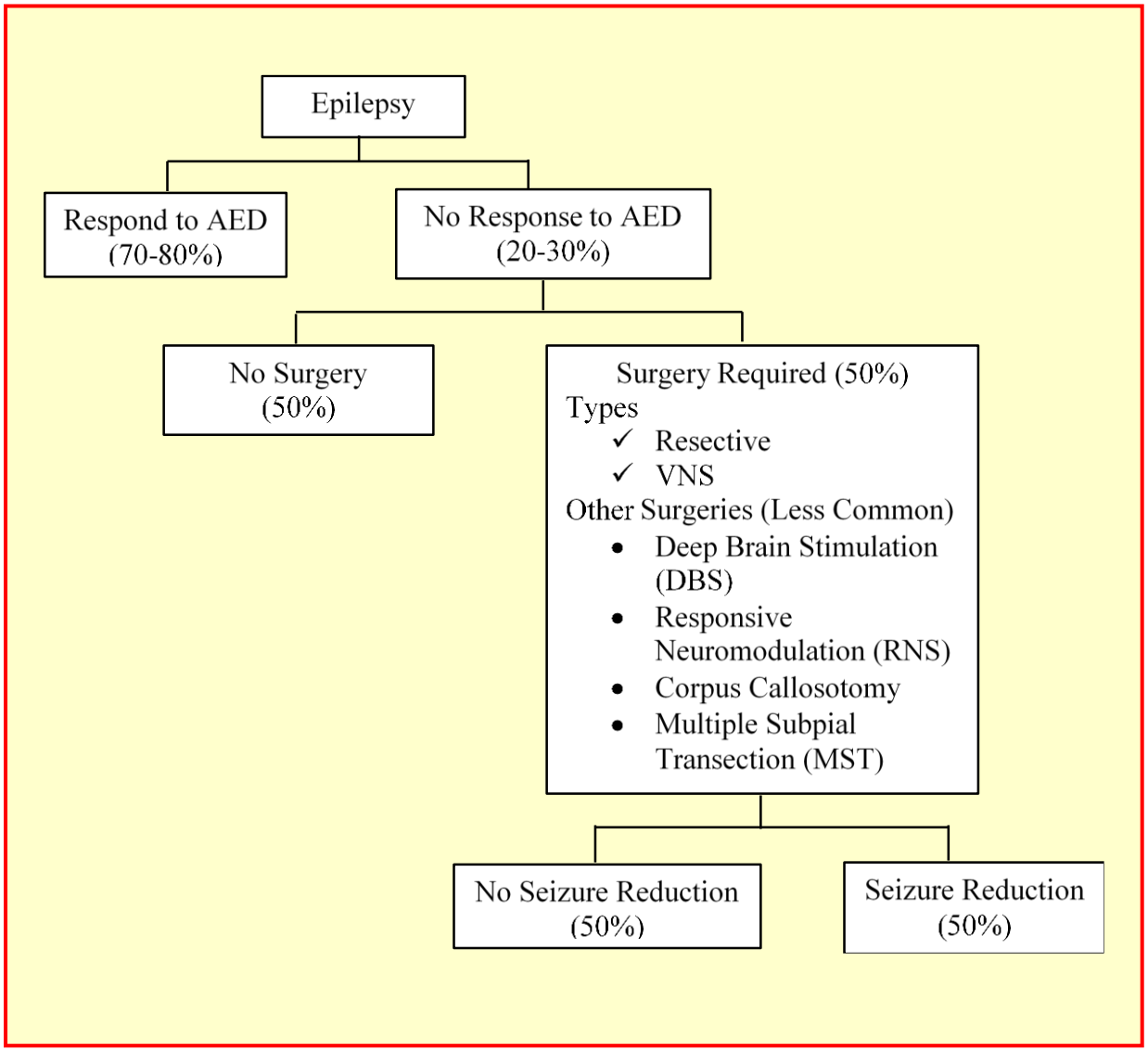
Source: Siddharth Kharkar. Epilepsy Surgery Cost in India 2023. Neuro+ Epilepsy and Parkinsons Clinic. https://drkharkar.com/epilepsy-surgery-cost-in-india-best-epilepsy-treatment-in-india/

Table 8. Cost for VNS pre-surgery investigations

Investigations	Indian Rupees (₹)
3 Tesla MRI	12,000
PET scan & PET-MRI fusion	15,000
Video-EEG monitoring (3 days)	30,000 x 3=90,0000
Functional MRI (fMRI)	12,000
Neuro-psychological & Psychiatry Assessment	6,000
Total cost	1,35,000

Source: Siddharth Kharkar. Epilepsy Surgery Cost in India 2023. Neuro+ Epilepsy and Parkinsons Clinic. https://drkharkar.com/epilepsy-surgery-cost-in-india-best-epilepsy-treatment-in-india/

Figure 12. Epilepsy treatment in India



Summary and Conclusion

- It is estimated that there are more than 10 million person with epilepsy in India. The prevalence of epilepsy is about 1% in India and the prevalence is higher in rural (1.9%) as compared to urban population (0.9%). The age adjusted prevalence ratio of active epilepsy is 4.7 per 1,000 population.
- With respect to incidence of epilepsy, there are very few incidence studies from India. The age standardised incidence rates reported was 27.3 per 100,000 population per year.
- There is a treatment gap in accessing health care facilities for diagnosis and treatment, and also not adhering to the prescribed antiepileptic drugs.
- The gap is reported to be influenced by various factors including lack of access to health facilities, lack of knowledge of antiepileptic drugs, poverty, cultural believes, stigma, poor health delivery infrastructure and shortage of trained professionals.
- In India, with less than 2,000 neurologists and estimated 5 to 6 million patients with active epilepsy. There is huge need to strengthen epilepsy services.
- The exact magnitude of medically intractable epilepsy in India is unknown. Intractable epilepsy is a seizure disorder in which a patient's seizures fail to come under control with treatment. These seizures are sometimes also called “uncontrolled” or “refractory.” The intractable groups were epileptogenic structural abnormalities such as mesial temporal sclerosis (MTS), dysembryoplastic neuroepithelial tumor (DNET) and perinatal hypoxic ischemic brain injuries.
- The magnitude of epilepsy treatment gap in India ranges from 22% in urban to 90% in village.
- Most people (70% to 80%) with epilepsy treated with medications called antiepileptic drugs.
- About 20-30% of persons developing epilepsy continue to exhibit chronic recurrent seizures despite optimal treatment with AEDs. These patients need on long-term follow-up will have their seizures unsatisfactory controlled by treatment with available AEDs. These patients also suffer from hard-to-treat depression (treatment resistant depression). It can be life threatening disease.
- One third of epilepsy patents (20% to 30%), the seizers are very difficult to control medication alone. This condition called drug resistant epilepsy (DRE).

- Another option of treatment is surgical intervention to remove the part of the brain that causes seizers 50% of non-response DRE patients (10% to 15%). However, not every one of this candidate for surgery.
- There are different kinds of Epilepsy surgeries. But about 80-90% of patients eventually get either resective (removal) epilepsy surgery or Vagus Nerve Stimulator (VNS) epilepsy surgery.

Vagus Nerve Stimulator (VNS) epilepsy surgery.

- VNS is an adjuvant treatment that has been approved by FDA for those suffer from focal partial epilepsy and that are not responding to antiepileptic medications.
- The exact cost of Vagus Nerve Stimulation (VNS) epilepsy surgery in India depends on the type of device selected. There are many types of VNS devices. But only 3 VNS devices are currently (Dec 2022) being used in India: Demipulse, Aspire SR and Sentiva.
- Though VNS results in higher successful seizure reduction rates as an adjunctive therapy to Anti-seizure medications for treating seizures in drug resistant epileptic patients, there are certain inevitable reasons for why VNS is not widely used in India. The reasons are given as follows.
    - The significant reason is that VNS is highly expensive compared to other treatments for drug-resistant epilepsy.
    - VNS is not used to treat all the patients who have epilepsy. Despite, VNS is only for patients who have drug resistant epilepsy. This refers to a condition in which standard anti-seizure medications fail to adequately control seizures.
    - VNS can help reduce seizure frequency and severity in some individuals with some extend (depends on conditions).
    - Due to the availability of more ASMs drugs which result in advantageous results, patients who go for VNS treatment is considerably low.
    - Moreover, only one in thousand eligible patients in India under goes epilepsy surgery, due to lack of awareness and willingness.
    - Majority of the centres in India utilized simple non-invasive pre-surgical evaluation strategy is to select their candidates or epilepsy surgery, techniques SPECT, PET, fMRI, diffusion tensor imaging tractography and invasive EEG

were available in major centres and were utilized by centres that did not possess them.

    - In addition to VNS, they have to put on AEDs, the number of drugs may be less and dosage may be come down.

- Total number of available drugs for epilepsy is increased in the last 20 years. At present, a newer ADE drugs are in broad spectrum, variety of generalized and focal seizures are controlled by these drugs.
- There are many adverse events that takes place followed by VNS. Some of them are, hoarseness or Voice Changes, coughing or throat irritation, paresthesia, headache, nausea, dyspnea, wound infections and allergic infections.
- VNS is typically considered when other treatment approaches have not provided adequate symptom control
- It is essential to note that the decision to use VNS is made on a case-by-case basis, and not all patients with drug-resistant epilepsy or treatment-resistant depression will be candidates for VNS.
- Medical professionals, including neurologists and psychiatrists, evaluate each patient's specific condition, medical history, and treatment response to determine whether VNS is a suitable option.
- Recent studies have shown that there is significant decrease in epilepsy related direct medical cost after implantation with VNS. This decrease is mainly due to an important decrease in number of hospital admission days after implantation. It is estimated that the cost of device can be paid back by savings in epilepsy related direct medical cost after 2.5 years.
- VNS is not an established treatment option for drug-resistant epilepsy. The wide use of VNS can vary depending on several factors, such as patient selection, adherence to treatment, and the underlying causes of epilepsy. Due to the cost effectiveness and increased treatment outcomes, VNS can be considered as the most suitable treatment for those who have drug resistant epilepsy.

Limitation

We did not consider the additional costs that ASM would acquire due to the injury, hospitalization and other associated costs due to unavailability in the Indian context. This would have underestimated the cost for ASM

Conclusion

In conclusion, though the systematic review and meta-analysis have shown VNS as a clinically effective adjunctive treatment for treating DRE, the cost-effectiveness analysis of VNS+ASM treatment for drug-resistant epileptic patients reveals that, it comes at a high cost. The ICER value of ₹7,45,798 for gaining a QALY of 0.4 years indicates that it may not be the most financially feasible option for a wider population. While VNS remains a valuable treatment for those who require it, its high expense makes it less affordable and may limit its widespread implementation in India.

Table-2. Review of literature

Ref	Author	Year	Study Area	Objective	Result	Recommendation
01.	Aalbers[13]	2016	The Netherlands	To evaluate the safety and efficacy of complete removal or replacement of the VNS system and provide an extensive description of our surgical technique.	Lead replacement is usually performed because of infection or device malfunction, the former being reported in 3–6 % of patients after initial implantation. Lead salvage by prolonged antibiotic therapy with or without removing the generator may be attempted, but the persistent infection will necessitate removing all hardware.	Complete removal or replacement of the VNS system including lead and coils is feasible and safe. Although initial results seem promising, further research and longer follow-up are needed to assess whether lead replacement may affect VNS effectiveness.
02.	Abubakr[37]	2008	USA	To retrospectively evaluated the long-term outcome of VNS therapy in patients with intractable epilepsy treated in the comprehensive epilepsy center of the New Jersey Neuroscience Institute.	This retrospective uncontrolled study illustrates continued seizure reduction after long-term adjunctive VNS therapy in patients with intractable partial-onset epilepsy.	Improving seizure control in the long-term supports the possibility of a sustained VNS effect on seizure reduction over time.
03.	Aihua[38]	2014	China	To evaluate the efficacy and safety of transcutaneous vagus nerve	The reduction in seizure frequency observed with t-VNS was correlated	In view of the significant reduction in seizure frequency and severity

Ref	Author	Year	Study Area	Objective	Result	Recommendation
				stimulation (t-VNS) in patients with pharmacoresistant epilepsy.	with seizure frequency and duration of epilepsy but not with age, seizure type, the number of AEDs, family history of epilepsy, MRI and EEG abnormalities, or the initial stimulation intensity. This suggests that t-VNS would be most suitable for those with higher seizure frequency and those who have had epilepsy for a long time	along with the improvement in the patients' mental states and QOL, we feel that t-VNS is an effective and safe therapy for pharmaco resistant epilepsy. Furthermore, we found that t-VNS may be most effective in those with high seizure frequency and a long history of epilepsy. Adverse effects included drowsiness and dizziness, which were relieved by either reducing stimulus intensity or discontinuing the stimulus.
04.	Batson[39]	2022	Multicentric	This systematic literature review (SLR) and meta-analysis examined the treatment efects of VNS Therapy at up to 2 years as an adjunct to ASMs for the management of adults with DRE based on the most up-to-date evidence from randomised	This systematic review and meta-analysis demonstrated that in people with DRE, adjunctive high-stimulation VNS therapy resulted in statistically significant reductions in seizure frequency without increasing the rate of SAEs or discontinuations when compared with adjunctive low-	VNS therapy resulted in reductions in seizure frequency without increasing the rate of SAEs

Ref	Author	Year	Study Area	Objective	Result	Recommendation
				controlled trials (RCTs) and comparative observational studies.	stimulation VNS Therapy/ASM/best medical practice.	
05.	Bauer[40]	2016	Germany	To demonstrate superiority of add-on therapy with “highlevel” tVNS (stimulation frequency 25 Hz) versus active control (“lowlevel” tVNS, 1 Hz) in reducing seizure frequency	tVNS had a high treatment adherence and was well tolerated. Superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this relatively small study, which might be attributed to the higher stimulation intensity in the control group. Efficacy data revealed results that justify further trials with larger patient numbers and longer observation periods.	Future trials should focus on comparison of tVNS and iVNS and should preferably include some period of video EEG monitoring for objective quantification of treatment results.
06.	Boon[41]	1999	Belgium	To evaluate efficacy of treatment in terms of seizure control and seizure severity was assessed one year before and after the implantation of a vagus nerve stimulator. Epilepsy-related direct medical costs (ERDMC) before	VNS is an effective and safe treatment for medically refractory epileptic seizures during the first months after implantation. It appears to be equally effective and safe in the first 2 to 3 years and lacks common side effects of AED's. Cost-benefit analysis is favorable. However, VNS	Future research should be aimed at elucidating the basic mechanism of action of VNS and identifying the best clinical responders

Ref	Author	Year	Study Area	Objective	Result	Recommendation
				and after the implantation were also compared.	should be considered a palliative treatment and only be performed after a thorough patient selection, excluding patients who may benefit from epilepsy surgery	
07.	Cramer[42]	2001		The purpose of the review is to provide comparable data in a standardized format for use by physicians and patients in the selection of treatment options.	Overall success rates fell into two general groups with ranges of 12–20% for gabapentin (GBP), lamotrigine (LTG), tiagabine (TGB), zonisamide and 27–29% for levetiracetam, oxcarbazepine, and topiramate (TPM). Summary Complaint Scores also fell into two general groups with ranges of −27 to −82 for GBP, levetiracetam, TGB, zonisamide and −113 to −205 for LTG, oxcarbazepine and TPM. VNS scores were in the lower or higher success and summary complaint categories depending on whether	Data allow comparisons among AEDs and VNS using similar data from standard types of clinical trials.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					scores from the pseudo-placebo group were subtracted from the high dose group.	
08.	Elger[43]	2000	Multicentric	Vagus nerve stimulation is associated with mood improvements in epilepsy patients.	This study revealed considerable and sustained VNS-associated mood improvements in patients with epilepsy. The reduction of depressive symptoms was more pronounced and seemed to be independent of seizure attenuation due to VNS	Further research on the functional integration of central and autonomous nervous systems, in which the vagus plays a decisive role, is needed.
09.	Elliott[44]	2009	USA	Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery.	Our results support efficacy and encourage using VNS and resective intracranial surgery in patients with TSC with refractory epilepsies. This study endorses the continued and expanded use of vagus nerve stimulation in the adult and pediatric TSC populations	VNS is a safe and effective treatment option for medically refractory epilepsy in patients with tuberous sclerosis complex. Nine of 11 patients (82%) experienced at least a 67% reduction in seizure burden. Lack of response to vagus nerve stimulation does not preclude subsequent improvement in seizure

Ref	Author	Year	Study Area	Objective	Result	Recommendation
						burden with intracranial epilepsy surgery
10	Englot[45]	2011	Multicentric	A meta-analysis of clinical studies examining the efficacy of VNS in reducing seizure frequency in epilepsy	Through a meta-analysis of VNS outcomes in treating medically refractory epilepsy, we found that VNS is effective in reducing seizure frequency by ≥ 50% in approximately 50% of patients, with a delayed benefit more than 1 year after surgery	Vagus nerve stimulation should be considered in patients in whom medical therapy has failed but who remain poor candidates for resection or who continue to experience seizures after resection.
11	Forbes[46]	2003	Multicentric	The cost-utility of vagus nerve stimulator (VNS) devices for medically refractory epilepsy has yet to be estimated.	Our model suggests that the economic argument against VNS implantation (with a 1 in 6 response rate) is weak, particularly given the clinical imperative to treat in an otherwise no-win situation of medically intractable epilepsy. As VNS is a last resort treatment, with a good chance of a meaningful reduction in seizure frequency, a case can be made for adopting the new technology.	There is not a strong economic argument against a programme of VNS implantation, although care should be taken to try and identify and treat those most likely to benefit

Ref	Author	Year	Study Area	Objective	Result	Recommendation
12.	Ghani [47]	2015	Multicentric	The aim of this study is to determine the effects of high and low stimulation paradigms on a responder rate of ≥50 and ≥75 % reduction in seizure frequency and associated adverse effects in adults and children	We estimate that the baseline cost per quality adjusted life year gained from a programme of six VNS implants, each with a battery life of 5 years, gaining 0.285 quality adjusted life years per annum, and averting £745 of health care costs to be £28 950	High stimulation is more effective than low stimulation in producing a greater reduction in seizure frequency in patients with medically and surgically resistant epilepsy
13.	Handforth[48]	1998	Multicentric	The purpose of this multicenter, add-on, double-blind, randomized, active-control study was to compare the efficacy and safety of presumably therapeutic (high) vagus nerve stimulation with less (low) stimulation	Patients receiving high stimulation had an average 28% reduction in total seizure frequency compared with a 15% reduction in the low stimulation group. The high-stimulation group also had greater improvements on global evaluation scores, as rated by a blinded interviewer and the patient. High stimulation was associated with more voice alteration and dyspnea. No changes in physiologic indicators of gastric, cardiac, or pulmonary functions occurred.	Vagus nerve stimulation is an effective and safe adjunctive treatment for patients with refractory partial-onset seizures. It represents the advent of a new, nonpharmacologic treatment for epilepsy.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
14	Zeiler et.al.[49]	2015	multicentre	To perform a systematic review on the insertion of VNS for refractory status epilepticus (RSE) and its impact on the control of RSE	A total of 28 patients were treated, Among them, 76% displayed cessation of RSE with VNS insertion in case of generalized RSE, , whereas 25% responded in case of focal RSE	The study cannot recommend the use of VNS for RSE. Further prospective study is warranted
15	Yoo & Panov et.al[50]	2019		Discusses the gap between evidence and practice and common misconceptions about epilepsy surgery and reviews the current diagnostic and therapeutic surgical options	Three randomized controlled trials comparing the medical versus surgical treatment for patients with drug-resistant epilepsy have shown the superiority of surgery in controlling seizures and improved the patient's quality of life. Further, responsive neurostimulation and VNS have also shown efficacy in seizure control that increases over time.	Patients with drug-resistant epilepsy should be referred to comprehensive epilepsy centres where thorough presurgical workup and surgical options can be provided. The gap between evidence and practice can be bridged by education, community outreach and provider's earnest efforts to improve the quality of life for patients with epilepsy

Ref	Author	Year	Study Area	Objective	Result	Recommendation
16	Xiong et,al[51]	2020		To identify factors predicting the effect of VNS therapy and to select patients suitable for VNS treatment	The effectiveness of VNS was confirmed by a number of studies. The factors post-traumatic epilepsy, temporal lobe epilepsy and focal interictal epileptiform discharges (IEDs) were favorable for the treatment of VNS while comprehensive IEDs and neuronal migration disorders were indicative of poor effect. Also, temporal lobe epilepsy was generally effectively controlled by this therapy and youngers seemed to get more benefit from VNS.	The conventional and other new factors should be analyzed further by more science and rigorous experimental design are needed to identify the clear correlation with the outcome of VNS therapy.
17	Adriana M. Workewych et.al.[52]	2020		To perform a scoping review of the literature to identify biomarkers of VNS response in patients with drug-resistant epilepsy.	Patient demographics, seizure data, and details related to biomarkers were abstracted from all studies. From the 288 records screened, 28 articles reporting on 16 putative biomarkers were identified. These were grouped	Further efforts are required to validate existing biomarkers to inform clinical decision-making.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					into four categories: network/connectomic-based biomarkers, electrophysiological signatures, structural findings on neuroimaging, and systemic assays. Differences in brain network organization, connectivity, and electrophysiological synchronicity demonstrated the most robust ability to identify VNS responders. Structural findings on neuroimaging yielded inconsistent associations with VNS responsiveness. With regard to systemic biomarkers, heart rate variability was shown to be an independent marker of VNS response, whereas inflammatory markers were not useful.	

Ref	Author	Year	Study Area	Objective	Result	Recommendation
18	Wheless James et.al.[53]	2018		To review the clinical data that support the device's efficacy in children, adolescents, and adults and also to review its side-effect profile, quality of life and cost benefits, and the impact the device has on sudden unexpected death in epilepsy (SUDEP). To discuss candidate selection and provide guidance on dosing and future models	Studies have demonstrated the efficacy of VNS therapy in adult and pediatric patients with pharmaco resistant epilepsy. VNS is safe and generally well tolerated; adverse events are typically related to the surgical procedure or stimulation itself. Cost-effectiveness studies indicate that VNS provides a substantial cost-savings benefit to healthcare systems.	The impact of VNS on mortality and SUDEP remains unsettled, with some data suggesting that it might reduce the risk of SUDEP.
19	Warwick et.al[54]	2007		To describe the efficacy of vagus nerve stimulation therapy in reducing seizure severity as well as improving the behavioral components of 23-year-old man's Asperger syndrome and also to review the current literature regarding epilepsy in autistic spectrum disorders.	The patient had behavioral regression that correlated with worsening of his intractable seizures	

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20	Uthman et.al[29]	2004		To perform a retrospective review of the safety, tolerability, and efficacy of vagus nerve stimulation (VNS) in 48 patients with intractable partial epilepsy.	Mean seizure frequency decreased by 26% after 1 year, 30% after 5 years, and 52% after 12 years with VNS treatment. Side effects were few and mild to moderate.	
21	Toffa et.al[55]	2020		To analyze the most meaningful available data describing the indications, safety and efficacy of the different approaches of VNS in clinical practice.	VNS is a relatively efficacious treatment in refractory epilepsy with various known treatment response predictors. The adverse effects decrease over time, in contrast to the benefits which continue to improve up to 6–24 months. If its indication was historically associated with epilepsy, this technique represents a promising treatment in several comorbid neuropsychiatric conditions such as headache and drug resistant depression. The implantable VNS remains the standard today, but interesting data have been published	The available publications reported data on small sample sizes. No study describing long-term follow-up was found for these non-implantable devices. There is a large methodological disparity that significantly limits the conclusion that can be drawn on the efficacy and safety of these devices

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					on the efficacy and safety of transcutaneous devices.	
22	Steven C Schachter et.al.[56]	2002		To discuss the clinical trials that provided evidence for the approval, long-term efficacy, efficacy in special populations and co-morbid conditions, and safety and tolerability.		Additional studies are suggested to further explore the capabilities of VNS therapy.
23	Santiago-Rodriguez et.al.[57]	2006		To evaluate the effects of two cycles of vagus nerve stimulation (VNS), 30 s/5 min and 7 s/18 s on the interictal epileptiform discharges	In 16 patients (80%), IED decreased during 30 s/5 min cycle (Group 1) and increased in 4 (Group 2). In Group 1, during the 30 s/5 min cycle the following variables showed a decrease: TIEDM, from 12.64 s to 9.62 s (p=0.001); IED/NIED index, from 0.53 to 0.31 (p=0.021), and IED duration, from 1.57s to 1.05s(p=0.015); whereas SFP duration increased from 20.06s to 37.73s (p=0.008). The decrease in	Our results are not enough to infer a determined mechanism of action of VNS upon the decrease in epileptiform activity and clustering effect in the EEG.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					IED was 41% and the increase in SFP 88%. In the 7 s/18 s cycle, only SFP had an increase, 72% ($p<0.043$). In Group 2, an increase in IED during both cycles was found. In the 30 s/5 min cycle, TIEDM increased 56% ($p=0.042$) and IED/NIED index 259% ($p=0.040$).	
24	Philippe Ryvlin et.al[58]	2014	Beijing (3 hospitals namely	To evaluate whether vagus nerve stimulation (VNS) as adjunct to best medical practice (VNS + BMP) is superior to BMP alone in improving long-term health-related quality of life (HRQoL).	VNS therapy as a treatment adjunct to BMP in patients with pharmacoresistant focal seizures was associated with a significant improvement in HRQoL compared with BMP alone.	Our findings demonstrate that the benefits of such therapy may be extended beyond the sole reduction in seizure frequency.
25	Rong et.al.[59]	2014	China	To examine the safety and effectiveness of transcutaneous auricular vagus nerve stimulation (ta-VNS) for patients with drug-resistant epilepsy.	In the pilot study, 47 of the 50 epilepsy patients completed the 24-week treatment; three dropped off. After 8-week treatment, six of the 47 patients (12%) were seizure free and 12 (24%) had a reduction in seizure	Similar to the therapeutic effect of VNS, ta-VNS can suppress epileptic seizures and is a safe, effective, economical, and widely applicable treatment option for drug-resistant epilepsy.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					frequency. In week 16 of the continuous treatment, six of the 47 patients (12%) were seizure free; 17 (34%) had a reduction in seizure frequency. After 24 weeks' treatment, eight patients (16%) were seizure free; 19 (38%) had reduced seizure frequency.	
26	Privitera et.al.[60]	2022		To overview the current evidence for the efficacy and tolerability of vagus nerve stimulation when used as an adjunctive treatment for people with drug-resistant partial epilepsy. To determine: (1) The effects on seizures of VNS compared to controls e.g. high-level stimulation compared to low-level stimulation (presumed subtherapeutic dose);	VNS for partial seizures appears to be an effective and well tolerated treatment in 439 included participants from five trials. Results of the overall efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation in reducing frequency of seizures. Results for the outcome "withdrawal of allocated treatment" suggest that VNS is well tolerated as withdrawals were rare.	The evidence on these outcomes is limited and of moderate to low quality. Further high quality research is needed to fully evaluate the efficacy and tolerability of VNS for drug resistant partial seizures.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
				and (2) The adverse effect profile of VNS compared to controls e.g. high-level stimulation compared to low-level stimulation	No significant difference was found in withdrawal rates between the high and low stimulation groups, however limited information was available from the evidence included in this review so important differences between high and low stimulation cannot be excluded . Adverse effects associated with implantation and stimulation were primarily hoarseness, cough, dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation.	
27	Polkey et.al.[61]	2003		To review the concepts of pathophysiology of epilepsy which underly the non-resective surgical treatment of epilepsy.	1. These non-resective surgical options rarely produce complete freedom from seizures but have been shown to significantly improve seizure control significantly and to be	Earlier surgical operations in this group probably now have a limited place.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					accompanied by improvements in behaviour, cognition and quality of life (QOL). 2. Stimulation, apart from economic considerations, has considerable potential benefit, not least of which is extending treatment to groups previously excluded. 4. Vagus nerve stimulation is now an accepted method of treatment which: a) should be applied after proper assessment; b) shows benefits in seizure control, behaviour and QOL; c) requires more rigour in its application. 5. Deep brain stimulation, although in its early stages, holds considerable potential.	
28	Pati et.al.[62]	2014		To review recent developments in the pathogenesis and treatment of pharmacoresistant epilepsy, placing these topics in clinical	The author hope that continued progress in genomics will lead to targeted development of disease modifying drugs that can impede or	Advances in informatics and genetics may be harnessed to predict which patients are likely to develop pharmacoresistance, to cure certain

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				context to facilitate and enhance the physician's ability to manage it.	reverse the process of epileptogenesis.	genetic epilepsies, and to individualize antiepileptic drug selection on the basis of each person's genetic profile.
29	Panebianco et.al[63]	2016		This article reviews the literature from 1988 to nowadays. Further, it discusses thoroughly the anatomy and physiology of vagus nerve and the potential mechanisms of actions and clinical applications involved in VNS therapy, as well as the management, safety, tolerability and effectiveness of VNS therapy.	VNS for partial seizures appears to be an effective and well tolerated treatment in adult and pediatric patients. People noted improvements in feelings of well-being, alertness, memory and thinking skills, as well as mood. The adverse effect profile is substantially different from the adverse effect profile associated with antiepileptic drugs, making VNS a potential alternative for patients with difficulty tolerating antiepileptic drug adverse effects.	

Ref	Author	Year	Study Area	Objective	Result	Recommendation
30	Navas et.al[64].	2010		The study presents two adult patients who underwent R-VNS. One of the patients improved dramatically after L-VNS, but the device had to be removed because of mechanical malfunction. This patient was thought to be at high risk for nerve injury if L-VNS reimplantation was done, thus R-VNS was chosen. In the other patient, L-VNS was first attempted, but the operation had to be stopped due to significant bleeding caused by the accidental tearing of an ectopic vein. Both patients had a marked reduction in their seizure activity and none of them had cardiac side effects from therapeutic R-VNS.	The author conclude that R-VNS therapy is an alternative, promising therapy for reducing seizure activity in those patients who cannot undergo L-VNS implantation. Close follow-up and frequent ECG monitoring is required to detect the presence of cardiac side effects.	

Ref	Author	Year	Study Area	Objective	Result	Recommendation
31	Hsiangkuo Yuan, Stephen D Silberste In[65]	2015	America	History and development of VNS, as well as recent progress in invasive and nVNS.	VNS was approved for the treatment of refractory epilepsy and later for the refractory depression. To date, several novel electrical stimulating devices are being developed.	Noninvasive VNS (nVNS) exhibits greater safety profiles and seems similarly effective to their invasive counterpart.
32	Yin Yan, et al [66]	2022	China	To describe the clinical features and possible mechanisms of FN induced by ASMs and to explore strategies for its treatment.	Timely reduction or discontinuation of ASMs and the use of antipsychotic drugs, the overall prognosis is good.	Exploring the factors related to FN caused by different ASMs can further improve clinicians' understanding of FN. The specific pathogenesis of FN needs further research in the future.
33	Stefan, et.al[67]	2021	Germany	To determine whether t-VNS offers a treatment option in drug-resistant epilepsy, we initiated a pilot study concerning safety and tolerability	t-VNS for pharmacoresistant epilep-sies indicates that t-VNS is safe, well tolerated, and practi-cable for long-term treatment. Some subjective complaintssuch as hoarseness occurred but are not easily explained byauricular nerve stimulation.	The noninvasive and reversible t-VNS approach mayoffer new options for improving patient care by use of well-tolerated adjunctive epilepsy treatment. In this pilot study,primary outcomes were safety and tolerability, and second-ary outcome was seizure reduction.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
34	Haiyang Wang et al[68]	2009	China (Harbin and Shanghai)	To observe the long-term interictal EEG changes induced by VNS, and to investigate the probable mechanism of action of VNS in achieving seizure control	Statistically significant difference of IEDs was seen when comparing the state of "deactivation" with the states of "activation" and "reactivation", respectively (P<0.01). However, there was no significant difference in IEDs between "activation" and "reactivation" (P>0.05).	VNS can induce progressive electrophysiological effect on epileptiform activity over time. This may reflect the mechanism of chronic action of VNS with desynchronization of EEG in achieving seizure control.
35	J Scherrmann et al [16]	2001	Europe	To study the clinical experience in a large patient series on vagus nerve stimulation (VNS).	VNS has to be considered an appropriate strategy for the add-on treatment of drug-resistant seizures, particularly in cases not suitable for epilepsy surgery.	No evidence was found for a differential outcome of initial standard cycle versus initial rapid cycle stimulation conditions.
36	Daniel San-Juan et al[69]	2019	Multicenter	To review the literature about the efficacy and safety of neuromodulation therapies in SE in humans.	Analyzed 27 articles (45 patients) with 4 different neuromodulation therapies. In ECT we found 80% rate of disruption of SE and 5% of adverse events was reported. Using iVNS 15/16 (93.7%) patients resolved the SE. All patients who underwent TMS	Case series and case reports suggest that neuromodulation therapies can abort SE in 80-100% of patients (Oxford scale and GRADE were level 4 and D) with a wide range of adverse effects, which claims for prospective

Ref	Author	Year	Study Area	Objective	Result	Recommendation
					and DBS aborted SE, however, 50% of patients with DBS had severe adverse events	studies on the relationship between efficacy and safety.
37	William E Rosenfeld et al[70]	2009	-	Medically intractable tonic and atonic seizures may be responsive to either vagus nerve stimulation (VNS) or corpus callosum section.	Callosotomy can be performed with low morbidity, and the prospect of perhaps greater relief from more injurious sudden falls may make it equally reasonable for patients willing to undergo a larger procedure. VNS is a less invasive, lower risk procedure, and these attributes argue reasonably for its consideration in the medically intractable patient.	There are low overall side effects associated with a VNS procedure, and there are no medication side effects
38	John D. Rolston et al[71]	2015	San Francisco, USA	To examine the evidence-based outcomes for both procedures, including their documented morbidities, and try to provide	Atonic seizures are debilitating, have a poor prognosis, and are incredibly difficult to control with antiepileptic medications. Two surgical treatments	There is a clear limitations in systematic reviews to guide clinical practice, these data suggest that CC might be more effective

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				guidance for the treatment of this challenging seizure subtype.	are primarily used to address atonic seizures: corpus callosotomy (CC) and vagus nerve stimulation (VNS). CC appears to offer significantly better chances of seizure freedom compared with VNS: 58.0% versus 21.1% (RR: 2.8; 95% CI: 1.5–5.1) and seizure control: 88.6% versus 52.6% of patients, respectively, (RR: 1.7; 95% CI: 1.2–2.3).	than VNS for atonic seizures.
39	Carlo Efisio Marras et al[72]	2020	Rome, Italy	To assess the clinical, organizational, financial, and economic impact of VNS therapy in drug-resistant epilepsies and to establish the congruity between costs incurred and health service reimbursement.	VNS reduces by at least 50% the frequency of seizures in 21–75% of subjects; the benefit of treatment might persist longer than 15 years of follow-up; and both adults and children could benefit from the treatment in 50–62% of patients	VNS appears to be an effective and well-tolerated treatment for partial seizures; at the time of publication, however, VNSs were utilized in all ages and different kinds of epilepsies, syndromes and etiologies.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
40	Lampros et.al[73]	2021	Multicenter	To study the systematic review of the literature to elucidate efficacy, adverse effects and technical features of t-VNS in patients with epilepsy.	Three studies reported a statistically significant ($p<0.05$) improvement in patients' quality of life and two studies reported statistically significant ($p<0.05$) seizure severity reduction. The most common side effect was headache (8.9%), followed by skin irritation at the placement site (7.1%) and nasopharyngitis (5.1%). No serious or life-threatening side effects were reported.	The results of this review suggest that patients with epilepsy could possibly benefit from the use of t-VNS. The present study also emphasizes the limitations of previous clinical trials concerning the applications of t-VNS in people with epilepsy and thus could be a guidance for the conduction of future trials.
41	Amar et.al[16]	1998	USA	To evaluate theoretical and practical issues attendant to this concept. To review the anatomic and physiological background arguing for clinical application of vagus nerve stimulation, discuss salient aspects of patient selection and the nuances of surgical technique, and present our	All operations were successful, uneventful, and without adverse postoperative sequelae. One patient was excluded from analysis because of inadequate seizure calendars. Of the seven patients initially assigned to high stimulation, the mean reduction in seizure frequency was 71% at 3 months and 81% at 18 months. Five	Vagus nerve stimulation has proven to be a safe, feasible, and potentially effective method of reducing seizures in select patient populations. However, the elements of strict definition for the application of the method require further study.

Ref	Author	Year	Study Area	Objective	Result	Recommendation
				observations of and results from application of the method.	(72%) of these patients had a greater than 75% reduction in seizure frequency, and one (14%) remained seizure-free after more than 1.5 years of follow-up. The mean reduction in seizure frequency among the low-stimulation group was only 6% at 3 months. No serious complications, device failures, or physiological perturbations occurred.	

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