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# Neuromodulation for Refractory Epilepsy

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**Abstract**

Three neuromodulation therapies, all using implanted device and electrodes, have been approved to treat adults with drug-resistant focal epilepsy, namely, the vagus nerve stimulation in 1995, deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) in 2018 (2010 in Europe), and responsive neurostimulation (RNS) in 2014. Indications for VNS have more recently extended to children down to age of 4. Limited or anecdotal data are available in other epilepsy syndromes and refractory/super-refractory status epilepticus. Overall, neuromodulation therapies are palliative, with only a minority of patients achieving long-term seizure freedom, justifying favoring such treatments in patients who are not good candidates for curative epilepsy surgery. About half of patients implanted with VNS, ANT-DBS, and RNS have 50% or greater reduction in seizures, with long-term data suggesting increased efficacy over time. Besides their impact on seizure frequency, neuromodulation therapies are associated with various benefits and drawbacks in comparison to antiseizure drugs. Yet, we lack high-level evidence to best position each neuromodulation therapy in the treatment pathways of persons with difficult-to-treat epilepsy.

**Keywords**

neuromodulation, vagus nerve stimulation, responsive neurostimulation, deep brain stimulation, drug-resistant epilepsy

## Introduction

It has been almost 50 years since the first attempt to control seizures with chronic electrical stimulation of the nervous system.[1] Yet, the first appropriately powered and designed randomized controlled trial (RCT) of neuromodulation for epilepsy, targeting the left vagus nerve, was only published in 1995,[2] leading to the approval by the U.S. Food and Drug Administration (FDA) of vagus nerve stimulation (VNS) as an adjunctive treatment for drug-resistant focal epilepsy in 1997. Since then, only 2 other neuromodulation therapies benefited from appropriate pivotal RCTs and were subsequently approved by the FDA within the last decade, deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) and responsive neurostimulation of the epileptogenic zone(s) (RNS).[3,4] In parallel, an upgraded VNS device, offering closed-loop tachycardia-responsive stimulation, has been made available in the last 5 years.[5,6] Approved neuromodulation therapies are all indicated in adults with drug-resistant focal epilepsy,[7] defined as the failure of adequate trials of 2 tolerated and appropriately chosen and used antiseizure medications (ASMs) to achieve sustained seizure freedom.[8] Yet, ANT-DBS requires the failure of 3 ASMs, and VNS benefits from broader indications in children down to age of 4 [7]. VNS is approved in much of the world; RNS only in the United States; and ANT-DBS in North America, Europe, and a few other countries.[7]

## Vagus Nerve Stimulation

In 2017, the indications of VNS were extended by the FDA to children ≥ 4 years old,[9] in agreement with the upgraded recommendations of the American Academy of Neurology (AAN)

which reported a 50% responder rate (50%-RR) of 55% in this age group.[10] Accordingly, a recent systematic review covering more than 100 pediatric VNS studies reported a pooled prevalence estimate for 50%-RR and seizure freedom of 56% and 12%, respectively.[11] Yet, the only double-blind RCT conducted in children aged 3 to 17 years was negative.[12] The AAN guidelines also concluded that VNS shows increasing efficacy over time.[10] A review of the literature and VNS registry data collating 8423 patients reported consistent long-term 50%-RR increasing up to 63%, and seizure freedom rate up to 8%.[13] However, duration of seizure-free periods remains unclear in most reports. Recent controlled and uncontrolled studies have confirmed the positive impact of VNS on quality of life (QoL). An open-label randomized trial showed that VNS therapy with best medical practice (BMP) was associated with a significantly greater improvement of QoL than BMP alone, with a mean gain of 5.5 points at 12 months.[14] A survey from 5000 VNS-treated epilepsy patients also suggested self-reported benefits in alertness, post-ictal state, cognition, and school or professional achievements.[15] In contrast, controlled studies failed to show a significant effect of VNS on comorbid depression in comparison to controls.[14,16-18]

The closed-loop VNS (AspireSR), which triggers vagus nerve stimulation upon detection of pre-defined (supposedly ictal) changes in heart rate, has now largely replaced standard VNS. Yet, true ictal tachycardia, defined as > 100 bpm with at least 55% increase or 35 bpm increase from baseline, was only observed in 16%-17% of seizures recorded with this device.[5,6] When using a more liberal threshold of ≥ 20% increase in heart rate, up to 66% of seizures could be detected but at the cost of 7 false detections per hour.[5,6] There is no controlled study comparing closed-loop to standard VNS. Yet, several uncontrolled studies reported improved seizure control following replacement of the latter by the former in 31% to 41% of cases.[19-21] Furthermore, one- to two-thirds of non-responders to standard VNS responded to the AspireSR.[19-21]

VNS has been used off-label in several epileptic disorders, in particular, generalized epilepsies. The AAN has recommended that VNS may be considered for Lennox-Gastaut syndrome (LGS),[10] where the 50%-RR was estimated at 55%.[10,22] Comparable benefits were reported in Dravet syndrome,[23] refractory idiopathic/primary generalized epilepsies,[24-29] and *CDKL5* disorder.[30] VNS has also been claimed to effectively control atonic seizures as an alternative to corpus callosotomy. However, a recent meta-analysis of 31 studies involving 533 children showed that callosotomy was more effective than VNS at a cost of greater adverse events, including twice as many reoperations and a 14% rate of symptomatic disconnection syndrome.[31] A recent meta-analysis reported 38 cases with refractory (RSE) or super-refractory (SRSE) status epilepticus, where limited or no alternative treatments was available, who were treated with VNS, including 28 whose status was controlled. However, RSE/SRSE ceased more than 10 days after implantation in half of these patients, calling into question the role of VNS in controlling status.[32]

The cost-effectiveness of VNS has been confirmed in several studies showing decreased hospitalization and emergency visits,[33-38] status epilepticus,[34,35] intensive care unit costs,[33] and antiseizure drugs' prescription,[37] but increased outpatient resource use.[36,38] Overall, most studies reported decreased direct healthcare costs following VNS therapy.[33-35,38,39] Yet, cost-savings largely vary between series and countries, with average direct costs of VNS treatment ranging as much as from 75 to 2333 dollars per month.[35,36,38]

While no new VNS-related side-effect has been reported, more evidence was collected regarding the significant risk of de-novo or aggravating sleep breathing disorders in up to 57% of patients.[40-42]

## Deep Brain Stimulation of the Anterior Nucleus of the Thalamus (ANT-DBS)

Following a positive pivotal RCT performed in 109 adult patients with drug-resistant focal epilepsy (SANTE trial), ANT-DBS was approved in Europe in 2010 and in the USA in 2018.[3] The long-term open-label extension study of the SANTE trial has shown improving efficacy in patients continuing ANT-DBS.[43] At 7 years of follow-up, the median reduction in seizure frequency and the proportion of 50% responders reached −70% and 74%, respectively.[43] In addition, 16% of patients enjoyed a seizure-free period ≥ 6 months during follow-up, but no long-term seizure freedom was observed.[44] Yet, 34% of patients discontinued ANT-DBS at the longest follow-up, with another 21% considered not evaluable due to missing data. If one considers all discontinuations and lack of evaluable data as treatment failures, the proportion of 50%-RR remains stable over time and is closer to 40% than 74%. Previous treatment with VNS does not seem to influence the chances of responding to ANT-DBS.[3,45] A few case reports have found ANT-DBS to be effective in controlling RSE[46,47] and antiGAD-associated TLE.[48]

ANT-DBS is associated with the classic risks of implant site infection and pain, the latter being reported in up to 20% of patients.[44] During RCT, stimulation of ANT was associated with significantly more frequent mood and memory complaints (15% and 13%, respectively) than sham stimulation (1.8%). At 7 years of follow-up, more than 30% of patients reported mood or memory disorders, with 10% expressing suicidality, two-third of whom had a past-history of depression prior to ANT-DBS treatment.[43] Yet, objective assessments do not necessarily support patients' subjective complaints,[49] and some improvement is reported over time[44] or with reduction in stimulation intensity.[50]

## Responsive Neurostimulation (RNS)

Following a positive pivotal RCT performed in 191 adult patients with drug-resistant focal epilepsy,[4] RNS was approved by the FDA in 2014. The long-term open-label extension study has reported up to 9 years of follow-up, showing a progressive increase in seizure control over time. In patients continuing RNS, the median reduction in seizure frequency and proportion

of 50%-RR reached −72% and 73%, respectively, while 28% of patients enjoyed seizure-free periods > 6 months.[51,52] Yet, 37% of patients discontinued RNS at the longest follow-up, with another 6% considered not evaluable due to missing data. As for ANT-DBS, if one considers all discontinuations and lack of evaluable data as treatment failures, the proportion of 50%-RR remains stable over time and closer to 40% than 73%. Improvement in QoL was also observed with RNS, including on cognitive and seizure worry subscores.[4,51]

While RNS typically targets cortical epileptogenic zone(s), it was also used successfully in a few patients to stimulate the thalamus, including the centromedian/ventrolateral thalamus bilaterally in a patient with drug-refractory Jeavons syndrome,[53] and the right anterior nucleus of the thalamus in an adult with childhood onset genetic generalized epilepsy.[54] Positive outcome of RNS was also reported in 4 patients with anti-GAD-associated TLE[55] and in 1 patient with SRSE.[56]

RNS provides unique intracerebral EEG data which can reliably give information on the epileptic activity of the recorded brain regions and offer additional benefits. In particular, RNS might demonstrate that some patients with suspected bitemporal epilepsy primarily suffer from a single or predominant seizure-onset zone, leading to successful unilateral temporal lobe epilepsy surgery.[57,58] Another application lies in the possibility to delineate patient's specific seizure cycles, which could enable clinically relevant seizure forecasting.[59,60] RNS-recorded data might also help to predict the long-term response to antiseizure drug shortly after its initiation.[61]

Infection at the RNS implant site amounts to 4% per surgical procedure and 12% of patients overall after 9 years of follow-up.[51] It usually only involves soft tissue, but still requires explantation in half of cases. Intracranial hemorrhage was reported in 3% of patients, with 1% associated with neurologic sequelae. In contrast with ANT-DBS, no cognitive side-effect was reported with RNS. On the contrary, some improvement was observed in neuropsychological performances, in relation to the brain regions stimulated.[62] Suicidality was reported in 10% of patients, 86% of which had a past history of mood disorders prior to RNS treatment.[51] This is to compare with the prevalence of suicidality reported in epilepsy in general, which often ranges between 20% and 35%.[63-65]

## Areas for Future Research

Despite the wealth of data collected through observational studies or clinical trials, several unanswered questions remain.

### *Impact on SUDEP Risk*

Two underpowered and 1 large-scale VNS studies, providing 6170 and 277,661 patient-years (PYs) of follow-up, respectively, investigated the evolution of the SUDEP rate as a function of the duration of VNS treatment.[66-68] Only the large-scale study reported a significant decrease of SUDEP rate over time.[68] However, due to the lack of appropriate controls, one cannot assess the proper role of VNS in mediating the reduction in SUDEP incidence. In a nationwide population-based case-control study, VNS treatment was associated with a significantly lower risk of SUDEP as compared to no such treatment with an odds ratio of .41 (95% CI: .17–.98).[69] As for other forms of neurostimulation therapy, the rate of probable or definite SUDEP in patients undergoing ANT-DBS and RNS was calculated at 2.9/1000 PYs (95% CI: .3-10.4) and 2.8/1000 PYs (95% CI: 1.2-6.7),[51] respectively, corresponding to the lower margin of the SUDEP figures reported in drug-resistant epilepsy.

### *Biomarkers Predicting Response to Therapy*

Reliable predictors of therapeutic response are lacking across neuromodulation options. Non-lesional epilepsy and generalized seizure type were found associated with greater VNS efficacy but with a very modest odds ratio,[13] while the role of age remains debated.[12,70-72] Several neurophysiological and neuroimaging predictors are being investigated but are not yet validated in clinical practice.[73-76] Similarly, we lack biomarkers to predict response to ANT-DBS, with some reports suggesting the potential value of temporal theta-band desynchronization,[77] hippocampal-evoked potentials,[78] and increased functional connectivity between ANT and the default mode network.[79] The exact position of ANT-DBS electrodes might also prove important, with some data suggesting better seizure control when stimulating the anterior half of ANT[80,81] or its junction with the mammillothalamic tract.[82,83] The transventricular lead trajectory appears more effective than the extraventricular one to reach the appropriate target, without difference in safety between the 2 methods.[84,85] No biomarker exists either to predict the clinical response to RNS.

### *Comparative Effectiveness*

No robust observational data or RCT data exist to meaningfully compare effectiveness across neuromodulation therapies. Two uncontrolled retrospective studies compared the effectiveness of RNS and VNS in a total of 53 patients, showing no significant difference in patients' profiles, median reduction in seizure frequency, and seizure-free rates.[86,87] Also, of interest is the proportion of patients who responded to ANT-DBS or RNS after having failed VNS. In the SANTE trial, 45% of patients had been previously treated with VNS, and these were found to equally benefit from ANT-DBS than the other patients.[3] Another series of 7 patients who failed VNS and were subsequently treated with ANT-DBS reported a 71% RR.[45] Similarly, patients who failed VNS demonstrated a similar response to RNS as those not previously treated with VNS.[4,51]

### *Seizure freedom Versus Remission*

Reported rates of seizure freedom in neuromodulation studies actually refer to periods of seizure-remission of varying duration, typically between 6 and 12 months, observed by the date of last follow-up during open-label extension phases of

clinical study. Considering that the estimated cumulative probability of 12-month seizure-remission is 33.4% at 7 years in patients with drug-resistant epilepsy using medical therapy alone[88] and that surgical series typically report complete seizure freedom since surgery (for example, an Engel score of 1 is equivalent to sustained seizure freedom since surgery and not terminal remission), ascertaining the true contribution of neuromodulation to observed remission 7 or 9 years after device implantation is difficult and will require further evaluation.

## Conclusion

Many neuromodulation therapies and brain targets have been proposed for epilepsy, but only 4 appropriately designed RCTs have been performed in the field.[2-4,89] Furthermore, these RCTs concentrated on demonstrating the antiseizure efficacy of active vs sham stimulation, with no evidence gathered to delineate the optimal timing for offering such therapies during the course of drug-resistant epilepsy or guide the choice or order of the different neuromodulation methods. Accordingly, neuromodulation should be currently primarily offered to patients with refractory epilepsy who are not, or who are poor candidates for curative epilepsy surgery. Decision regarding the type of neuromodulation should be discussed with patients and caregivers based on a fair presentation of the expected risks and benefits associated with each type of therapy.

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