Epilepsy & Behavior 91 (2019) 25–29

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Long-term outcome in neurostimulation of epilepsy

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ARTICLE INFO

Article history:
Received 25 April 2018
Revised 6 June 2018
Accepted 6 June 2018
Available online 30 June 2018

Keywords:
Epilepsy
Neurostimulation
Neuromodulation
Vagus nerve stimulation
Deep brain stimulation
Closed-loop stimulation

ABSTRACT

For patients with pharmacoresistant focal epilepsy, neurostimulation offers nonpharmacological strategies to improve seizure control. Vagus nerve stimulation (VNS), deep brain stimulation of the anterior thalamic nuclei, and responsive neurostimulation (RNS) are approved therapies which have shown efficacy in randomized short-term trials. Controlled data from prospective studies are needed to confirm reports on stable or even increasing evidence from studies with longer follow-up and to confirm that neurostimulation may offer advantages also regarding cognitive tolerability and sudden unexpected death in epilepsy (SUDEP)-risk. Here, a review of long-term outcomes is given, highlighting both achievements in terms of efficacy and tolerability and limitations of conclusions thereon related to an uncontrolled data basis and decreasing cohort sizes.

This article is part of the Special Issue? "Individualized Epilepsy Management: Medicines, Surgery and Beyond".

1. Introduction

Seizures in about one-third of patients with epilepsy respond insufficiently to available antiepileptic drug (AED) treatments 1–3. For this patient group, nonpharmacological treatment strategies are required. Epilepsy surgery has convincingly proven superiority over pharmacotherapy once one or two AEDs have failed and a focus can be resected 4–6. Not all patients are amenable for epilepsy surgery, however, as the epileptogenic brain area may be difficult to identify, may overlap with eloquent brain areas, or may encompass several brain regions. Furthermore, not all patients accept resective brain surgery as a treatment option, and they would rather opt for minimally invasive and reversible treatment strategies.

Neurostimulation has accordingly gained interest in the treatment of pharmacoresistant epilepsy, and diverse stimulation techniques have become available for clinical treatment and are being investigated in animal models and in clinical trials [7]. The mechanisms of action of neurostimulation differ depending on targets and stimulation parameters used and are incompletely understood so far. One interesting finding, differing from the outcome following pharmacotherapy or resective surgical treatment, is an increase in efficacy with longer observation periods, which has been reported for several types of neurostimulation. This has prompted a discussion as to whether neurostimulation has short- and long-term effects based on different modes of action, a direct anticonvulsive action and a long-term neuromodulatory effect on epileptogenic networks which becomes effective only over prolonged periods of time. In a chronic disease like epilepsy, such long-term effects are of critical importance for ranking treatment options and for patient counseling on chances and risks of selected treatments.

During recent years, new data on long-term effects of clinical treatment with vagus nerve stimulation (VNS), stimulation of the anterior nucleus of the thalamus (DBS-ANT), and responsive focus stimulation (RNS) have become available, which are reviewed in the following. Data were derived from articles identified by a systematic PubMed research using the terms “stimulation”, “epilepsy”, “long-term”, and “outcome”. Results are summarized for the stimulation type, and some general aspects are discussed.

2. Outcome of neurostimulation

2.1. Vagus nerve stimulation

Vagus nerve stimulation has become available in Europe since 1994 and in the US since 1997 for the treatment of pharmacoresistant focal epilepsy, and has also been approved for the treatment of generalized epilepsies in Europe. By peripheral stimulation of the vagus nerve, brain stem nuclei including the N. coeruleus and raphe nuclei are activated via the N. tractus solitarii, and an anticonvulsant efficacy is assumed to rely on widespread projections of these nuclei [8]. During recent years, a VNS device capable of sensing electrocardiogram (ECG), extracting heart rate and inducing stimulation if a moving threshold is surpassed (“Aspire”), has become available [9].

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https://doi.org/10.1016/j.yebeh.2018.06.011
1525-5050/

Functionality of this device has been shown only as to the detection of tachycardia but not on the specific effects of ictal stimulation. So far, no long-term outcome data have been published, which would provide evidence of a superiority of additional tachycardia-based VNS over conventional preprogrammed stimulation.

Short- and medium-term assessments have recently suggested superiority of VNS efficacy as compared with optimized pharmacotherapy [10, 11]. Some studies have reported constant efficacy over periods of several years (e.g. [12]) or even an improved efficacy over prolonged treatment periods [13,14]. Similar findings of increased efficacy over time were reported in a number of patient cohorts (15–22; see, however, [23,24]). Cukiert et al. [25] reported that efficacy may vary over time depending on the seizure type studied.

Long-term data assessing the safety of VNS have mostly reported no new adverse effects over time except from device-related complications like spontaneous turn-offs and stimulator malfunction in 2.8%, disconnection in 2.8%, and lead fracture in 11.9% after a mean follow-up time of 5 years [26]. Only rarely have new clinical adverse effects been reported to arise intraindividually over long treatment periods, like a new occurrence of AV blockade after 12 years of VNS treatment [27].

Recently, data on sudden unexpected death in epilepsy (SUDEP) rates have been reported based on the VNS registry of Cyberonics/Livanova [28]. Reported SUDEP cases were less frequent than expected in patient cohorts with pharmacoresistant epilepsy, and became significantly lower in patients in whom follow-up data were in the registry over longer periods of time, going down from 3.1/1000 patient years in year 1 to 2.4/1000 patient years in year 10 of follow-up in patients aged 10–54 years. This finding is of interest as the cohorts in whom VNS is offered over-represent difficult-to-treat patients considered at high risks of complications like SUDEP. Unfortunately, the data are not based on a predefined patient cohort undergoing long-term prospective assessment but on entries in the company's database with unclear reporting bias and complex assessment of SUDEP cases.

Like with tachycardia-based additional activation of the VNS system [9], there are neither long-term outcome data on efficacy nor on patient acceptance for transcutaneous VNS [29].

2.2. Stimulation of the anterior thalamic nuclei

Since finalization of the randomized, blinded SANTE trial on bilateral anterior thalamic nucleus stimulation in the treatment of focal epilepsy [30], thalamic stimulation has become an approved therapy in Europe, Canada and Australia, Canada, and Australia [31], but not in the US, as the primary objective of the trial had been missed. Thalamic stimulation is assumed to interfere with propagation of epileptic activity via the Papez circuit and by modulation of activity in limbic areas [32].

In the controlled double-blind phase of the SANTE trial, the median seizure reduction in the stimulation had increased from −21.3% following electrode insertion to −40.4% in the third month of treatment, compared with −14.5% in a nonstimulated control group. Subsequently, patients underwent long-term follow-up with continued or newly established stimulation, yet without control of cotreatments. A five-year follow-up study [33] reports an increased efficacy in the subgroup of patients remaining on stimulation until year five from a median of 41% seizure reduction at one year follow-up to a median of 69% after five years, and responders increased from 49% to 68% after five years. The group of patients remaining on treatment, however, declined from 105 after one year to 64 after 5 years, assumedly enriching responders. In an intent-to-treat analysis, which avoids enrichment of responders, efficacy of thalamic stimulation increased from a median seizure reduction of 40% after year one to 50% at year five, suggesting that efficacy remains stable or increases following one year of thalamic stimulation. Eleven out of 75 patients continuing thalamic stimulation at 5 year follow-up had been seizure-free during the last 6 months of follow-up, which is remarkable in view of the high degree of pharmacoresistance that seizures of patients entering the trial previously had shown. Long-term efficacy was similar in patient subgroups with temporal and frontal lobe epilepsy and in those who had undergone epilepsy surgery or VNS prior to thalamic stimulation, the latter suggesting independent mechanisms of action involved in these neurostimulation approaches. Stable long-term efficacy of ANT-DBS with a median seizure reduction around 70% and a seizure freedom rate of 24.1 % for tha last 6 months of follow-up was reported in a single center cohort [34].

So far, the analysis of stimulation parameters did not give evidence which stimulation parameters were best suited at a group level. Data from an ongoing prospective, industry-sponsored European registry on the effects of stimulation of the anterior thalamic nuclei in epilepsy (MedtrOnic *Registry* for *Epilepsy,* “MORE”) have not yet been made accessible to the public so far.

Long-term data have recently been published on mood and cognition during anterior thalamic stimulation. During the double-blind phase, 8/54 patients reported depressed mood under thalamic stimulation as compared with 1/54 in the control group, and 7/54 patients in the stimulation arm reported memory problems vs. 1/54 in the control group. At a group level, these individual reports were not reflected in significant changes in scores of standardized mood questionnaires (POMS), although 8.2% of patients, mostly with a history of depression, reported suicidal ideation during treatment. Careful monitoring of mood at in individual level thus remains mandatory.

Aside from questionnaires, neuropsychological test batteries comprising standard tests of declarative memory like the California Verbal Learning Test and visual memory tests were also applied over the course of treatment [35]. Long-term follow-up for up to 7 years did not give evidence of significant alterations in the subgroup of patients continuing treatment. Unfortunately, no cognitive test scores are given on those patients who discontinued treatment and, in particular, on those who had subjectively reported memory impairments during the randomized phase. Other adverse effects like infections or pain at the implant site have only been reported cumulative over the whole period of device implantation, thus not allowing the differentiation between early and late events. Overall, ANT-stimulation was associated with local complications (pain: 20.9%, implant site infection: 12.7%, device infection: 8.2%, and device dysfunction: 5.5%) as well as with stimulation-induced paresthesias (22.7%) [33]. The SUDEP rate over the 5-year follow-up period was 3.9/1000 patient years, which is in the range expected in the patient group with highly pharmacoresistant epilepsy.

2.3. Responsive neurostimulation

Long-term follow-up of patients undergoing neurostimulation has also been provided for responsive neurostimulation (RNS). The RNS was approved by the Food and Drug Administration (FDA) in 2015 based on a randomized controlled trial performed in the US, which had shown superior efficacy of RNS over a control arm with sham stimulation [36]. Here, stimulation of one or two epileptic foci is performed via a device implanted into the skull which continuously analyzes electroencephalogram (EEG) data, uses feature- and threshold-based seizure detection, and provides stimulation in response to electrographic patterns classified as ictal [37].

Long-term assessment showed stable seizure reductions and responder rates over years 3–6 both for neocortical and for mesiotemporal epileptogenic regions ([38,39, Fig. 1) which was superior to early stimulation results during the blinded phase and during years 1–2 of treatment. Again, declining numbers of patients analyzed are not controlled for in these data.

Two years after RNS treatment, data on cognition and quality of life were reported. Interestingly, in parallel to a reduction in seizure frequency, domain-specific improvements were reported depending on the stimulation site: improved declarative memory as to verbal learning and a trend towards improved delayed recall was found in patients with mesiotemporal stimulation, and improved naming with neocortical

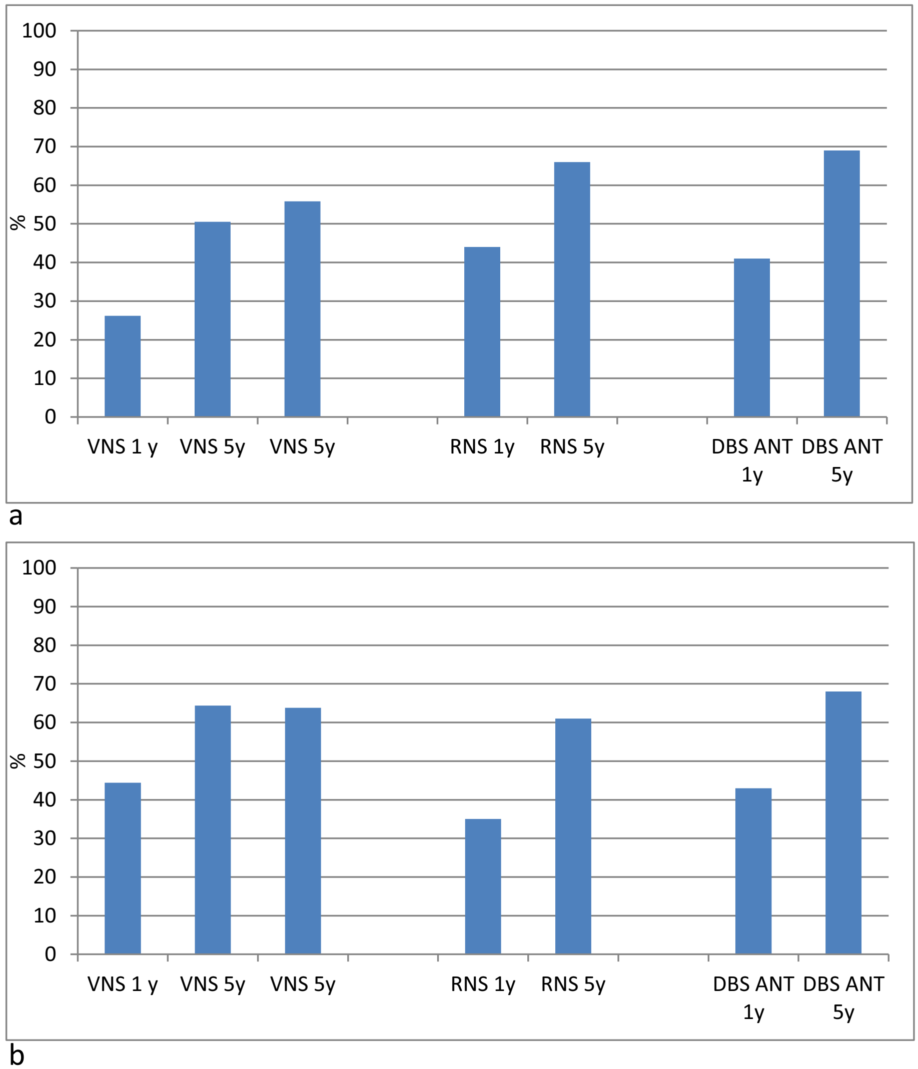

Fig. 1. a. Reported reductions in median seizure frequency over 5 years as compared with the first year. Note that outcomes are gathered without blinding of patients or treating physicians, without control groups, and with changing cotreatments and are not adjusted to the drop in patient numbers remaining under stimulation. (Based on data from [17, 18, 20, 33,38,41]). b. Reported responder rates over 5 years as compared with the first year. Note that outcomes are gathered without blinding of patients or treating physicians, without control groups, and with changing cotreatments and are not adjusted to the drop in patient numbers remaining under stimulation. (Based on data from [17, 18, 20, 33,38,41]).

stimulation [40]. Remarkably, no patients treated by responsive hippocampal stimulation had a memory decline under stimulation treatment. Improvements were also reported in several domains of quality of life, including reduced seizure worry and discouragement due to the health condition, improved social and physical functioning, and subjective ratings of attention and memory [41].

The SUDEP rate in 707 patients undergoing RNS treatment for a mean period of 2.9 years was 2.0 [42], again lower than expected in the difficult-to-treat patients undergoing RNS implantation.

Recently, casuistic evidence has been published and showed that long-term alterations in efficacy of stimulation are paralleled by a reduction in the number of seizure detections. Kokoszka et al. [43] reported about a patient who had an increasing efficacy of seizure termination with increase in stimulus amplitude over time, as reflected by an evidence of desynchronization of ictal patterns during which stimulation was performed, and by a reduced clinical seizure duration in a setting of corticothalamic electrode placement.

Evidence for long-term changes indicating neuromodulation beyond effects on an individual seizure came from casuistic findings. Reduced detection rates of ictal patterns were found in two responders to RNS [43]. Neuromodulation was suggested to be independent on the efficacy to terminate ictal patterns in a case reported by Bruzzone et al. [44]. This case showed no obvious effect of ictal responsive stimulation on ictal seizure patterns as assessed by the RNS device and scalp EEG but had an effect on seizure frequency as evidenced by an increase in seizures when turning off the stimulator and a decrease when reactivating the device.

3. Discussion

Outcome data of neurostimulation show that it is an effective, yet palliative approach. More than half of the patients benefit from this, yet only 5–23% of patients achieve seizure-free periods; this is clearly inferior to the efficacy of epilepsy surgery. The evaluation of surgical options prior to use of neurostimulation approaches thus remains recommended [45]. Long-term data on neurostimulation outcome do, however, provide evidence for a sustained, possibly increased, efficacy in patients with pharmacoresistant epilepsy, and the degree of seizure reduction and responder rates compares favorably with medical treatment. Relatively low SUDEP rates as recently published for RNS and VNS may further support consideration of neurostimulation in patients with highly pharmacoresistant epilepsy.

Of note, almost all available data on long-term outcome discussed are based on open-label treatment, not controlling for changes in cotreatments (in particular changes in the antiepileptic comedication) and without control groups assessing the spontaneous long-term course of epilepsy without alterations in the treatment regime. When early effects of VNS therapy were compared with those of the best medical treatment, outcome was considered similar by Sherman et al. [46] and Hoppe et al. [47], yet better by Ryvlin et al. [10] who reported superiority of VNS treatment one year after its initiation; here, the best medical treatment control group did not show any improvement, which appears exceptional in view of other studies comparing, e.g., epilepsy surgery with AED treatment (e.g., [48–50]) and considering the fluctuating course of epilepsy. There is thus a clear need for prospective assessments of neurostimulation with control groups ([51]; see also a negative controlled short-term assessment of VNS efficacy by Klinkenberg et al. [52]).

A lack of control of cofactors affecting conclusions based on long-term outcome data in patient cohorts is exemplified by a publication of Elliott et al. [20] reporting an increase in seizure reduction over time during VNS treatment from 38% after 6 months to 78% after 120 months in a long-term follow-up of 65 patients. These 65 patients with available follow-up until 120 months were preselected; however, 15 patients (18.7%) were excluded: 6 patients who died during follow-up, 6 patients who had had device removal, and 3 lost to follow-up. Within this analyzed subcohort of 65 patients, 6 patients (9%) had undergone epilepsy surgery during this period, and – contrary to expectations with a growing efficacy of VNS – drug load of the cohort increased from 2.7 to 3.2 during the follow-up with unclear changes in AEDs and their possible effects on overall treatment efficacy. In this line, Alexopoulos et al. [23] found markedly reduced "improvements" in long-term outcome when performing a last visit carried forward analyses instead of reporting outcomes on the subgroup of patients remaining on stimulation treatment only.

Comparative analyses of the three approved neurostimulation approaches [53] showed similar tendencies for increasing rates of seizure reduction and responders within the patient subgroups which continued treatment (Fig. 1a, b). Overall, few patients became long-lasting seizure-free under treatment, yet seizure-free periods of 6 months at defined endpoints were achieved in 5.5% of patients with VNS, in 16% with ANT-DBS, and in 23% with RNS, suggesting that a subgroup of patients had major benefit from treatment. Even if all the long-term data provided face methodological problems related to patient selection and uncontrolled cotreatments, data for all neurostimulation approaches suggest that treatment efficacy is at least stable over time or may improve over periods of years. Studies on the mechanisms of long-term neurostimulation effects are needed, including assessments of gene expression and of alterations in functional connectivity in brain network architecture.

So far, none of the neurostimulation devices are known optimal stimulation paradigms. As the feature space is vast (including stimulation intensity, frequency, pulse width, pulse form, duty cycle, and timing), a systematic assessment is difficult in human clinical trials. Aside from experimental settings (e.g., [54]), human intraindividual long-term data might offer one approach to assess relevant parameter changes. It remains to be seen if central databases as available for the RNS device or registries as ongoing for thalamic stimulation will provide evidence for stimulation settings which can improve treatment outcomes in the future.

The available closed-loop ("responsive") neurostimulation suffer from two critical issues: the specificity of detection-based interventions and the efficacy of ictal stimulation. In RNS, the implementation of detection algorithms and the thresholding approach lead to >99.9% detections and interventions at times without clinically manifesting seizures, questioning the closed-loop approach. This may be due to a tuning of algorithms towards sensitivity; early detection based on thresholding of simple EEG-derived features, however, is inferior to modern classification approaches derived from machine learning or deep learning strategies [55–57]. Similar to the RNS system, the algorithm for tachycardia-based VNS has a low specificity for ictal heart rate increases and leads to markedly increased duty cycles if a high sensitivity is aimed at. Presently, it remains an open question if RNS or tachycardia-based VNS exert their efficacy by aborting seizures or rather by frequent interventions with a long-term neuromodulatory effect (e.g., [21,43]).

Overall, long-term outcomes of neurostimulation do not show major differences in seizure control between the approaches chosen. Accordingly, the choice may depend on considerations as to whether the region of seizure origin is well defined as required for RNS, if frontotemporal limbic areas play a role which may favor ANT-DBS, and multifocal epilepsy or extended regions of epileptogenesis may favor the choice of VNS [58]; of note, evidence for these considerations remains to be provided. Tolerability issues are another consideration in selecting a neurostimulation approach: whereas VNS and RNS appear to have no negative cognitive effects (with RNS even showing cognitive gains in specific domains), thalamic stimulation may have negative effects on memory at least in some patients, even if this, in the long-term, did not become significant at the level of the group of patients continuing treatment. VNS is perceived by patients and observable to others whereas intracranial stimulation techniques occur unnoticed, yet require intracranial placement of electrodes. A well-informed patient's judgment may thus critically contribute to the choice of treatment.

Conflict of interest

Dr. Schulze-Bonhage reports grants from NIH, BMBF, DFG, EU and BIAL and personal fees for advice of lectures from BIAL,PRECISIS, EISAI and UCB.

Acknowledgments

This review was supported by the Excellence Cluster BrainLinks-BrainTools (DFG, Grant # EXC 1086).

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