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Vagus nerve stimulation in people with epilepsy and intellectual disability—English version

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Abstract

Background: In view of the still high rate of pharmaco-resistance in epilepsy, it is crucial to shed light on the non-pharmacological forms of therapy. Consideration of the patient group with epilepsy and intellectual disability is important for several reasons: it is a relevant patient group with an even higher proportion of drug-resistant courses than in people with epilepsy and normal intelligence. Resective epilepsy surgery is often not possible due to multifocal or diffuse brain damage. There are specific syndromes to consider as well as cognitive and behavioral peculiarities. Vagus nerve stimulation is discussed as a possible palliative therapy option.
Aim of the work: Based on a literature search, the present work sheds light on the importance of vagus nerve stimulation in the treatment of people with epilepsy and mental disabilities with special consideration of specific syndromes.
Results: Depending on the syndrome, the nature of the studies and the observational period, different outcomes of vagus nerve stimulation are observed. Compared to people with epilepsy and normal intelligence, there is a similar spectrum of side effects.
Discussion: Vagus nerve stimulation may be discussed in people with epilepsy and intellectual disability, bearing in mind the palliative nature of the intervention and the need for implantation of a device. It should be remembered that magnetic resonance imaging can only be used to a limited extent in the presence of an implanted vagus nerve stimulator.

Keywords
Intellectual disability · Tuberous sclerosis · Lennox-Gastaut syndrome · Dravet syndrome · Non-pharmacological therapy

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Despite the fact that a large number of new antiepileptic drugs have been approved in recent years, the proportion of people with treatment-resistant epilepsy has remained essentially unchanged at approximately 30% [9]. In the group of people with intellectual disabilities, the prospect of freedom from seizures is even poorer. According to a cross-sectional study from the residential care sector conducted at the Bodelschwingh Foundation Bethel, Germany, of 675 persons with epilepsy and disability, 240 (36%) became seizure-free [17]. The seizure-free rate decreased from 44% of people with learning disabilities to 39% in mild mental retardation, 33% and 32% in moderate and severe mental retardation, respectively, and to 22% among people with the most severe mental retardation. It is currently impossible to predict whether drugs approved with a special indication for rare diseases (orphan drugs) will change this, even though some of these drugs are used in a precision-medicine approach.

As an alternative to the treatment of drug-refractory epilepsy, resective epilepsy surgery should be considered first. The indication for this should be considered in cases of proven pharmacore-

sistance. This usually requires presentation to a specialized center. Mental retardation is not a contraindication to presurgical video-EEG monitoring [8]. In a large study from Sweden on the results of epilepsy surgery, just over 60% of patients with an IQ above 70, almost 40% with an IQ between 50 and 69, and just over 20% (but this was only four patients) with an IQ below 50 were seizure-free at 2 years postoperatively [22].

When resective epilepsy surgery is not possible in patients with drug-refractory epilepsy, palliative surgical approaches include callosotomy and neurostimulation procedures such as chronic vagus nerve stimulation (VNS; [16]). Vagus nerve stimulation involves the implantation of a device under the skin on the left side of the chest that emits electrical pulses. The device is connected via a subcutaneous electrode cable to an electrode placed in the neck in a spiral around the left vagus nerve (CN X). Current intensity, frequency, duration, and pauses can be varied. Modern devices additionally take into account changes in heart rate during the seizure.

Due to limited data on transcutaneous VNS, especially in relation to people with intellectual disabilities, the present review refers to subcutaneous (invasive) VNS.

Mechanisms of action and animal experimental data

Describing the basics would exceed the focus of this article. Reference is made here to relevant review articles [16].

Clinical studies

Five studies led to the approval of VNS as an adjunctive treatment for epilepsy by the U.S. Food and Drug Administration and to approval in the European Union.

Two small prospective, single-blind pilot studies with a total of only 14 patients (E01, E02; [33]), showing a mean decrease in seizure frequency of 46.6% at 14–35 months with antiepileptic medication that remained constant, including five patients (35.7%) with at least a 50% reduction in seizure frequency, were followed by a prospective, nonblinded study (E04) of 24 patients with generalized seizures and generalized interictal epilepsy-type activity on EEG [20]. This included seven patients with idiopathic generalized epilepsy according to the terminology of the time and 17 with symptomatic epilepsy. Mean seizure frequency decreased by 46%. In all, 11 patients experienced a reduction in seizure frequency of more than 50%. For symptomatic epilepsy, the mean seizure frequency decreased by 40%, while for idiopathic epilepsy, the mean seizure frequency decreased by 60%. A later onset of epilepsy and a higher seizure frequency before the onset of VNS were predictive of a higher reduction. The subsequent studies E03 [13] and E05 [14] were randomized double-blind trials involving 114 patients and 196 patients, respectively. Two stimulation paradigms were compared: high-level stimulation and low-level stimulation. High-level stimulation was undertaken with settings that were assumed to be therapeutically effective on the basis of the pilot studies. Low-level stimulation was also assumed to be ineffective but nevertheless perceived by the patient.

Study E03 showed a mean seizure frequency reduction of 24.5% with high-level stimulation compared with 6.1% in the low-level group, and 27.9% vs. 15.2% in the E05 study. The group of responders, i.e., patients with a seizure frequency reduction ≥ 50%, comprised 31% with high-level stimulation and 13% with low-level stimulation in the E03 trial, while the percentages in the E05 trial were 23% and 16%, respectively. The results of both studies showed significant improvements in the high-level group compared to the low-level group.

Studies E01–05 transitioned to a pooled long-term study in terms of open-label follow-up [24]. In accordance with the open nature of the study, treatment was not blinded, and the stimulation parameters were initially the same as for high-level stimulation. Over the course of the study, these could be individually adjusted. Medication could also be changed; 454 patients entered this long-term study.

The number of responders increased from 23% at 3 months to 37% at 12 months and to 43% at 36 months. As in open-label drug trials, it must be borne in mind that patients who did not respond well may often have left the study. After 3 years, a retention rate of VNS treatment of 72% was still observed.

In the context of this review article, five studies with a total of 118 patients are of particular interest; these studies largely included people with symptomatic focal or generalized epilepsy, including Lennox–Gastaut syndrome (LGS). At the last follow-up, an average reduction in seizure frequency of between 51% and 56% was observed compared with baseline before the start of VNS. The number of responders ranged from 38 to 55%. After the first year, the numbers were significantly lower [3, 5, 28, 32, 34]. Favorable results were noted in children, including patients with tuberous sclerosis complex (TSC) and LGS [2].

In a Bethel collective of 234 patients (of whom 197 were evaluable) who were not differentiated by intelligence level, 37 (18.8%) reported positive efficacy. This could be a reduction in seizure frequency, severity, series, need for on-demand medication, or grand mal seizures. The experience in this group of patients was not as positive as reported in the literature [30].

While a positive influence on cognition could not ultimately be confirmed [6, 11, 15], the data on the quality-of-life parameter during VNS stimulation appear inconsistent. Minor improvements in quality of life are sporadically described, e.g., patients with an at least 50% reduction in seizure frequency showed slightly more improvements in quality of life than did patients with a lower reduction in seizure frequency [11]. Since VNS can positively affect depression, there is a corresponding approval for the method in relevant cases.

Studies taking into account people with intellectual disabilities

Of 436 patients (of whom 52.8% were adults) in a large Norwegian registry study, 52.8% had an intellectual disability [19]. These patients had a reduced chance of successful VNS compared to people with normal intelligence.

A meta-analysis of VNS in children found lower efficacy in children with intellectual disabilities [27]. However, the authors found no prospective controlled trials.

A recent study investigated the feasibility and safety of outpatient VNS implantation in 26 adult patients with severe intellectual disability. The patients had various forms of epilepsy, and all patients could be discharged postoperatively on the same day of the procedure. Over a follow-up period of 1 month, no patients required hospitalization for postoperative complications [23].

Tuberous sclerosis complex

In a recently published retrospective study of 17 patients with TSC enrolled over as many as 11 years between 2008 and 2019, a rate of 70.6% was seen for 50% responders over an observation period of 0.5–10 years [31].

Overall, very high responder rates are reported, albeit retrospectively with small patient numbers [26]. According to a literature review, the use of VNS in children with TSC is not advocated on the basis of a cost–benefit analysis [12]. However, there are also positive data both in terms of a 50% responder rate (72%) and improvements in cognitive function, behavior, and quality of life [36]. A caveat to this is that this is a retrospective analysis of 11 patients. There are other studies with similar numbers of cases and similar reports of success [21].

Dravet syndrome

Again, there is a small study on 22 patients with drug-resistant Dravet syndrome who received a VNS implant. Responder rates were high (36.4% at 1 year, 54.5% at 2 years, and 63.2% at 3 years). It is reported that one of three seizure-free patients became seizure-free after 30 months with VNS. Here, attributing success to the form of therapy is undoubtedly challenging [35].

A review of 13 studies with a total of 68 patients (11 single-center case series, one multicenter retrospective analysis, and one case report) found a responder rate of 52.9% [10].

Lennox–Gastaut syndrome

In a recent analysis, better outcomes were seen for callosotomy in patients with LGS compared to VNS, but at higher costs for callosotomy [1]. In a recent meta-analysis including 17 studies, 178 of 370 patients (48.1%) were found to have experienced a reduction in seizure frequency at the final time point of the study [29]. No improvement was seen over a longer period of time. Callosotomy was more effective in comparison. Combinations of different surgical techniques including resective procedures were considered, but with very small case numbers.

Adverse effects

The first thing to consider, of course, is the possible effects of surgery (wound infection, hematoma, left vocal cord paralysis, infections). Transient hemiparesis, transient urinary incontinence, transient aphasia, and apraxia have been reported [18]. Stimulation-related symptoms include hoarseness, throat irritation, and pharyngeal paresthesia. Hoarseness, cough, pharyngeal pain, and dyspnea have been observed, with marked decreases after prolonged periods [4]. Central and obstructive apnea and hypopnea have been reported [25]. Bradyarrhythmias and asystole have been described in case reports [7].

Summary and conclusion

The study data give an indication of the palliative efficacy of vagus nerve stimulation (VNS) in the treatment of epilepsy. This is also true for epilepsy in people with intellectual disabilities. The potential benefits need to be weighed against the need for surgical intervention with—relatively low—risks, the side effects, and the fact that implantation of a VNS device limits the use of modern and ever-improving magnetic resonance imaging capabilities. In the future, the method of VNS will be measured against the success of new antiepileptic drugs, especially those using precision medicine approaches.

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Declarations

Conflict of interest. C. Brandt has received speaker's or consultancy fees from Angelini/Arvelle, Eisai, GW Pharmaceuticals, Johnson & Johnson, UCB Pharma and Zogenix.

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