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Vagus nerve stimulation in refractory and super-refractory status epilepticus – A systematic review

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ABSTRACT

Rationale: Refractory status epilepticus (RSE) is the persistence of status epilepticus despite second-line treatment. Super-refractory SE (SRSE) is characterized by ongoing status despite 48 h of anaesthetic treatment. Due to the high case fatality in RSE of 16–39%, off label treatments without strong evidence of efficacy in RSE are often administered. In single case-reports and small case series totalling 28 patients, acute implantation of VNS in RSE was associated with 76% and 26% success rate in generalized and focal RSE respectively. We performed an updated systematic review of the literature on efficacy of VNS in RSE/SRSE by including all reported patients.

Methods: We systematically searched EMBASE, CENTRAL, Opengre.eu, and ClinicalTrials.gov, and PubMed databases to identify studies reporting the use of VNS for RSE and/or SRSE. We also searched conference abstracts from AES and ILAE meetings.

Results: 45 patients were identified in total of which 38 were acute implantations of VNS in RSE/SRSE. Five cases had VNS implantation for epilepsia partialis continua, one for refractory electrical status epilepticus in sleep and one for acute encephalitis with refractory repetitive focal seizures. Acute VNS implantation was associated with cessation of RSE/SRSE in 74% (28/38) of acute cases. Cessation did not occur in 18% (7/38) of cases and four deaths were reported (11%); all of them due to the underlying disease and unlikely related to VNS implantation. Median duration of the RSE/SRSE episode pre and post VNS implantation was 18 days (range: 3–1680 days) and 8 days (range: 3–84 days) respectively. Positive outcomes occurred in 82% (31/38) of cases.

Conclusion: VNS can interrupt RSE and SRSE in 74% of patients; data originate from reported studies classified as level IV and the risk for reporting bias is high. Further prospective studies are warranted to investigate acute VNS in RSE and SRSE.

Introduction

Status epilepticus (SE) is a condition resulting from either the failure of seizure termination mechanisms or from initiation of mechanisms which enable abnormally prolonged seizures and can have long-term consequences including neuronal death, neuronal injury, and alteration of neuronal networks [1]. The annual incidence of SE in adults is 36.9/100.000 in a Western European cohort [2]. The incidence is highest in children, elderly and in resource poor countries with up to 82 episodes/100.000/year [3–5]. Refractory SE (RSE) is defined as persistence of SE despite treatment with benzodiazepines, used as first-line treatment, and one antiepileptic drug administered as second-line treatment; super-

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refractory SE (SRSE) is characterized by ongoing SE despite 48 h of anaesthetic treatment [6,7]. SE represents a significant burden on health care providers: one study estimated the annual costs of SE in Germany at 200 million € [8]. The majority of costs and resource consumption associated with SE can be attributed to RSE and SRSE which require significantly longer hospitalization and more intensified treatment and monitoring [9]. Furthermore RSE and SRSE are associated with high case fatality: one-year mortality rates for RSE and SRSE were found to be 22% and 36% respectively in a recent retrospective analysis of national ICU admissions in Finland [10].

Due to the high case fatality in RSE and SRSE, off-label treatments, many approved for treating refractory epilepsy but without evidence of efficacy in RSE or SRSE are often administered [11,12]. Anaesthetics pose the backbone of RSE/SRSE therapy. It is however unclear which is the optimal choice of anaesthetic as controlled or comparative studies are lacking [7]. An expert review on outcomes RSE/SRSE treatments stresses the lack of outcome data in RSE/SRSE and neccessity of urgent remediation but also takes into account that suffciently-powered randomized or controlled studies are not feasible in relation to the many therapies used in combination in this uncommon and heterogenous condition [13].

Vagus Nerve Stimulation (VNS) was approved for adjunctive treatment of drug resistant epilepsy (DRE) in Europe in 1994 and in the USA in 1997 and involves intermittent electrical stimulation of the left cervical vagus nerve by means of an implanted helical electrode connected to a pulse generator (VNS Physicians Manual). Evidence for seizure termination by VNS is limited to experimental studies [14] and case reports [15,16]. Although it has been documented that VNS reduces the occurrence and re-occurrence of SE [17,18] it remains a matter of debate whether acute implantation of VNS in a patient with SE may be beneficial in terminating the episode of SE. Single case-reports and small case series of acute VNS implantation in RSE were included in a systematic review published in 2015; VNS was associated with RSE cessation in 76% of general and 26% of focal RSE [19]. We performed an updated systematic review of the literature on efficacy of VNS in RSE/SRSE by including all reported patients.

Methods

The results of the present systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and adheres to a structured review protocol [20].

Search strategy and article selection

Two authors (F.B. and M.D.A.) performed a search of EMBASE, CENTRAL, Opengre.eu, ClinicalTrials.gov, and PubMed databases using the following search strategy: ("VNS" OR "vagal nerve stimulation" OR "vagus nerve stimulation") AND ("status epilepticus" OR "NORSE" OR "FIRES" OR "Febrile infection-related epilepsy syndrome"). The same search strategy was used to search for conference abstracts from AES and ILAE meetings of the past 5 years. The authors then independently excluded non-relevant articles based on review of the full-text articles before comparing selected publications reporting on outcomes of patients with any type of status epilepticus that were implanted with a vagus nerve stimulator published in English language were included. Upon uncertainty of inclusion of a publication an additional author was consulted.

Data extraction

From each article the primary endpoint of cessation or not of the RSE/SRSE episode in which VNS was implanted was extracted. A positive outcome was defined as either cessation of the acute RSE/SRSE episode in which a VNS was implanted and no report of later death or a significant (>50%) reduction in the most debilitating seizure type or seizure-freedom/no reoccurrence of status epilepticus. The following data were collected if reported: focal or generalized RSE/SRSE convulsive or non-convulsive SE, age, sex, epilepsy type (in case of a patient with epilepsy), epilepsy etiology, SE etiology, treatments prior to and after VNS, duration of SE prior to VNS and time to cessation, VNS parameters and long-term outcome.

Classification of articles

Grading of level of evidence was carried out using the American Academy of Neurology's (AAN) classification scheme [21]. The AAN defines a Class I and a Class II study as a randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment with a Class II study lacking one criterion a–e of Class I [21] or being a prospective matched cohort study that meets b–e Class I. Class III trials are all other controlled trials (e.g. natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed or derived by objective outcome measurements. Class IV studies are those not meeting Class I, II, or III criteria including consensus or expert opinion.

Statistical analysis

Primary outcomes are expressed as the proportion of cases describing acute cessation of RSE/SRSE or a positive outcome. Descriptive statistics (median, range, mean, standard deviation) of duration of RSE/SRSE pre- and post VNS implantation were computed as well as of VNS parameters.

Results

Study selection and level of evidence

The described search strategy yielded 396 publications (Fig. 1) of which 33 were duplicates. Of the remaining 363 publications 335 were excluded for not reporting on outcomes of patients with status epilepticus treated with VNS and therefore being irrelevant to this analysis. The remaining 28 publications were screened leading to exclusion of two relevant abstracts that reported on the same patient [22,23] as one full-text article included in this analysis [24]. Finally, 26 articles describing 45 patients with status epilepticus treated with VNS were included in this analysis [24–48]. 38 patients underwent acute implantation of VNS in an episode of RSE/SRSE. Five cases describe VNS implantation in refractory epilepsia partialis continua, one in refractory electrical status epilepticus in sleep and one in acute encephalitis with refractory repetitive focal seizures. According to the AAN level of evidence classification scheme all studies included in this analysis were classed as level IV evidence.

Primary endpoints

Acute VNS implantation was associated with cessation of RSE/SRSE in 74% (28/38) of acute cases (Table 1a). Cessation did not occur in 18% (7/38) of cases. In 3 cases, only long-term outcomes (outcomes after the SE episode) were reported hence whether acute VNS implantation was associated with the cessation of the

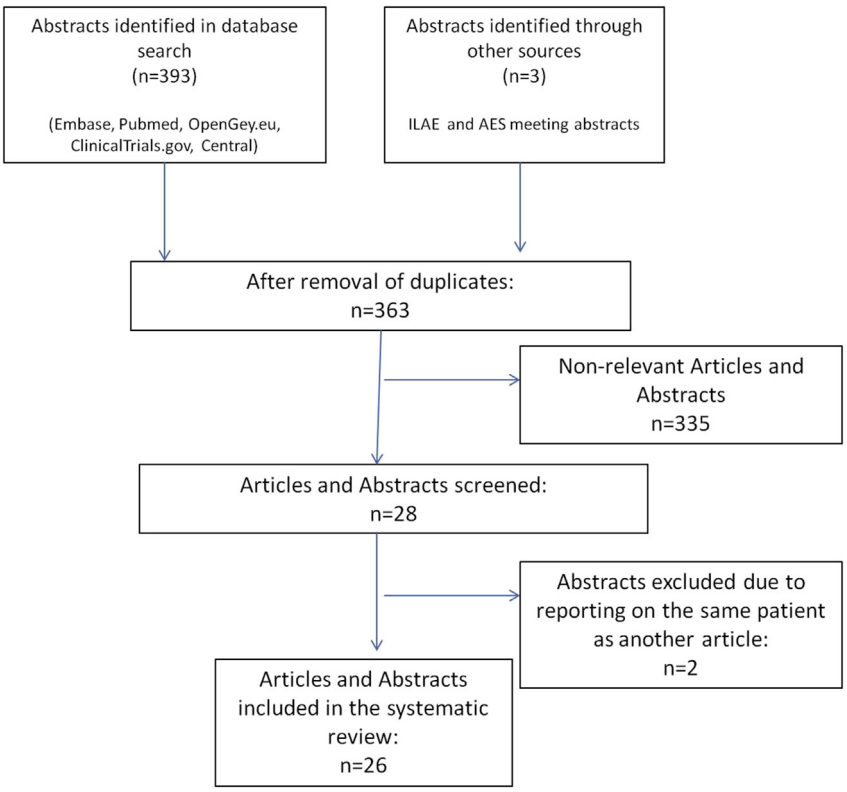

Fig. 1. Search strategy.

RSE/SRSE was unclear. Positive outcomes occurred in 82% (31/38) of cases. For the patients receiving a VNS for non-emergent or electrical forms of RSE/SRSE, positive outcomes were reported for all patients (Table 1b).

Etiologies and treatments

Etiologies for RSE/SRSE were reported for 45% (17/38) of the acute cases and ranged from AED withdrawal in people with epilepsy (n = 5) to different causes of encephalitis (n = 6). A fever was reported in 7 cases and 13 patients suffered from an epileptic encephalopathy. For 22 cases treatments prior to VNS were reported, however not all of these reports use of benzodiazepines and AEDs leading to the question whether reporting of treatments covers the refractory phase only. Use of propofol was reported in 11 patients, use of phenobarbital in 16, 8 received midazolam, 4 lorazepam and 1 diazepam. Steroids were used in 3 cases, ketamine in 5, intravenous immunoglobulins in 2, ketogenic diet in 2 and plasma exchange or plasmapheresis in 2 patients.

Duration of RSE/SRSE pre- and post VNS implantation

The duration of the RSE/SRSE episode pre- and post VNS implantation is reported in 34% (13/38) and 50% (19/38) of cases respectively (Table 2). The median duration of the RSE/SRSE episode prior to VNS implantation was 18 days (range: 3–1680 days) and median duration post VNS implantation was 8 days (range: 3–84 days).

VNS parameters

Information on programming of VNS devices was reported in 50% (19/38) of the acute cases. Median output current was 1.5 mA (range 1–3 mA), median frequency was 30 Hz (range 20–30 Hz), median pulse-width 500 μsec (range 250–500μsec) and median duty cycle was 16% (range 10–58%) indicating rapid titration of stimulation.

Adverse events

Not all included studies reported adverse events which prevents a systematic analysis thereof. One patient experienced recurrent bradycardia and hypotonia (under co-medication with thiopental) on post-operative day 4, leading to asystole and resuscitation without complications. The patient continued on VNS with no further episodes. One patient with Febrile Infection-Related Epilepsy Syndrome (FIRES) experienced intermittent bradycardia after dose escalation up to 1.75 mA over 36 h. One patient with EPC experienced seizure aggravation when stimulation was increased from 0.25 mA to 0.5 mA which was reversed at reduction to 0.25 mA. Four deaths were reported (11%); all of them due to the underlying disease and unlikely related to VNS implantation. One of the four deaths occurred in a 25 year-old man 13 days after acute VNS implantation for NORSE, which initially interrupted the SRSE episode for 72 h. There was however a reoccurrence of SRSE which was fatal. The second death occurred a month after VNS implantation in an infant in whom the episode of SRSE could not be terminated. The second death occurred in a child with FIRES 15 days after VNS implantation which failed to interrupt the episode of SRSE leading to severe bilateral cortical edema and multi-organ failure. The third death occurred after a GTCS in an 82 year-old man one year after VNS implantation.

Discussion

With all its limitations this systematic literature review found acute VNS implantation to be associated with cessation of RSE/SRSE

Table 1a
Cases of RSE/SRSE treated with acute VNS implantation.

Author	Publication Type	Patient #	Sex	Age	Epilepsy Type	New Onset (NO) or Epileptic Patient (EP)	in EP -Etiology	SE Etiology	Cessation of SE Y/N associated with VNS	Long-term Outcome
Kurukumbi et al., 2019	Case Report (IV)	1	M	25		NO		Unknown encephalitis	y	Died 13 days after VNS implantation due to reoccurrence of SRSE
Grioni et al., 2018	Case Series (IV)	2	F	1.3	Focal motor	EP	left hemimegalencephaly		Y	>90% seizure reduction
		3	F	1.4	Focal motor	EP	deletion of chromosome 1 (1q43q44).		Y	Free of spasms under VNS monotherapy (no AEDs)
		4	M	0.6	Focal motor	EP	Severe Migrating Epilepsy		N	Died in palliative care at 0.7 years
		5	M	1.3	Focal (myoclonic)	EP	nonketotic hyperglycinemia		Y	>90% seizure reduction
Yamazoe et al., 2017	Case Report (IV)	6	M	24	Multi-focal (tonic-clonic, cognitive)	NO		anti-GluR encephalitis?	Y	Seizure-free
Pichon et al., 2016	Case Series (Conference Abstract) (IV)	7	M	0.83	Focal	EP	Hypoxic ischemic encephalopathy > right temporal resection			Seizure-free
		8	M	2	generalized	EP	Progressive mitochondrial encephalopathy			50% seizure reduction
		9	M	6	Focal	EP	Left Mesial temporal sclerosis			Seizure-free
Yazdi et al., 2016	Case Report (IV)	10	M	67	Multi-focal (cognitive))	NO		evacuation of a right-sided spontaneous subdural hematoma	Y	1 seizure in 5 years
Alsaadi et al., 2015	Case Report (IV)	11	M	46	Multi focal non-motor	NO		anti-NMDA encephalitis	Y	seizure-free
Hoang et al., 2014	Case Report (IV)	12	F	40	Multi-focal	NO			N	Perampanel initated 3.5 months after admission leading to RSE cessation
Donahue et al., 2013	Case Series (Conference Abstract) (IV)	13		5.3	not reported				Y	
		14		5.3	Multi-focal				Y	
		15		5.3	Multi-focal				N	
		16		5.3	Multi-focal				N	
		17		5.3	Multi-focal				N	
Howell et al., 2012	Case Series (IV)	18			Multi-focal	NO		FIRES	N	Treatment withdrawal and death on day 29
Lin and Ko 2012	Case Series (Conference Abstract) (IV)	19	F	19	Multi-focal	NO		anti-NMDA encephalitis	Y	
		20	M	49	Multi-focal	NO		unknown encephalitis	Y	
Soto et al., 2012	Case Report (Conference Abstract) (IV)	21	F	4	Generalized (tonic-clonic) & focal	EP	perinatal asphyxia, hypoxic isquemic encephalopathy		Y	free of GTCS
Shatzmiller et al., 2011	Case Report (Conference Abstract) (IV)	22	F	19	Generalized non-motor	NO		anti-NMDA encephalitis	N	patient improved 1 after four pulses of cylcophosphamide (after VNS)
O'Neill et al., 2011	Case Report (Conference Abstract) (IV)	23	M	23	Genralized (tonic-clonic, myoclonic)	EP	JME		Y	>75% seizure-reduction
Soto et al., 2009	Case Report (Conference Abstract) (IV)	24	F	15	Focal to bilateral tonic clonic	EP	perinatal meningitis		Y	free of GTCS
Thielemann et al., 2009	Case Report (Conference Abstract) (IV)	25	M	23	Generalized myoclonic			AED withdrawal	Y	improvement beyond pre-hospital baseline (1 nocturnal seizure per week vs multiple daily before)

De Herdt et al., 2009	Case Report (IV)	26	F	7	Generalized (tonic-clonic) & focal	EP	Peri-natal pathology including thalamic hemmoragic infarct	Y	Seizure-free
Zamponi et al., 2008	Case Series (IV)	27		1.6	Multi-focal	EP	catastrophic epilepsy in childhood	Y	
		28		1.6	Multi-focal	EP	catastrophic epilepsy in childhood	Y	
		29		1.6	Multi-focal	EP	catastrophic epilepsy in childhood	Y	
Patwardhan et al., 2005	Case Report (IV)	30	M	30	Generalized (tonic-clonic) & focal	EP	AED withdrawal	Y	Seizure-free
Zimmerman et al., 2005	Case Series (Conference Abstract) (IV)	31	M	20	Multi-focal	EP	AED withdrawal	Y	
		32	M	82	Multi-focal	EP	AED withdrawal	Y	died from GTCS 1 year later
		33	F	64	Multi-focal	EP	AED withdrawal	Y	
Malik et al., 2005	Case Series (Conference Abstract) (IV)	34		1.16	Focal (atonic, motor)	EP		Y	significant seizure reduction
		35		3.5	Generalized (atonic, tonic-clonic myoclonic)	EP		Y	significant seizure reduction
		36		10	Multi-focal	EP		Y	no seizure reduction
Skaff et al., 2001	Case Report (IV)	37	F	27	Focal	NO	Human papiloma virus B19	Y	(not clear in w hich order TPM, LRZ and VNS were given after 52 days
Winston et al., 2001	Case Report (IV)	38	M	13	Generalized (tonic, myoclonic, absence)	EP	LGS?	Y	>50% seizure reduction

in 74% (28/38) of cases with a median duration of the RSE/SRSE episode post VNS implantation of 8 days (range 3–84 days). Cessation was found to not occur in 18% (7/38) of cases and four deaths were reported (11%); all of them unlikely related to VNS implantation. Positive outcomes (either cessation of the acute RSE/SRSE episode in which a VNS was implanted and no report of later death or a significant (>50%) reduction in the most debilitating seizure type or seizure-freedom/no reoccurrence of status epilepticus) occurred in 82% (31/38) of cases.

With high case fatality [2,10] RSE and SRSE represent devastating conditions, however beyond anaesthetics, the basis of RSE/SRSE therapy, it is unclear which therapeutic approach is most optimal as controlled or comparative studies are lacking [7].

Next to internalization of synaptic GABA receptors and increase of surface NMDA-receptors, induction of epigenetic and genetic changes leading to altered expression of proteins with excitatory and inhibitory properties (e.g. substance P) initiating hours and days after SE onset are considered to contribute to refractoriness towards agents targeting classic anti-epileptic targets [49,50]. On this basis, new treatment approaches are being investigated with non-drug approaches potentially offering particular benefit in drug-refractory SE. Many of these treatments and their current level of evidence have been summarized in a recent systematic review by Arya et al. [51]. A Class I trial found therapeutic hyperthermia not to be more effective than standard care in treating RSE/SRSE and raised safety concerns [52]. Despite the inherent challenge of a pre-surgical evaluation in an ongoing episode of SE a few small series describe treatment of RSE/SRSE by resective surgery: SRSE ceased in 10 out of 10 patients with 7/10 patients being seizure-free at 7 months [53]. A recent review of case reports describing use of electro-convulsive therapy to treat RSE/SRSE found electrographic resolution in 6 out of 8 cases, but recovery to baseline in only 2 patients [54]. Isolated reports describe also successful use of anterior thalamic deep-brain stimulation to treat RSE/SRSE [55]. Similar to VNS, the ketogenic diet (KD) has been administered to patients with RSE and SRSE in clinical practice however with fewer cases reported than for VNS. A recent case-series of 14 paediatric patients with RSE treated with KD found electrographic seizure resolution along with $\geq$50% suppression in 10/14 patients within 7 days of starting the KD. Eleven out of 14 patients could be weaned off continuous infusions within 2 weeks of starting KD [56]. Despite what one may classify as positive outcomes in these small series, use of KD in RSE and SRSE is cautious: the authors note that KD was under-utilized, as the 14 patients derived from a cohort of 239 RSE patients and there was a median delay of 14 days after SE onset, before KD was initiated.

Long-term studies in heterogeneous DRE populations show that VNS elicits a >50% reduction in seizure frequency in approximately 60% of patients [57,58]. Anti-ictal and anti-epileptogenic mechanisms of action of VNS have been investigated extensively, however it remains unclear which of the many effects of VNS are responsible for clinical seizure reduction and cessation in epilepsy patients. It is well documented that VNS increases firing rates and metabolic activity in the nucleus tractus solitarius (NTS) of the brainstem and in the structures directly connected to it [59]. Of these connections the dorsal raphe nucleus (DRN) and locus coeruleus (LC) of the brainstem are of special interest as they represent the main serotonin and norepinephrine producing sites of the brain and increased levels of these mono-amines and their metabolites have been found both in patients treated with VNS and in preclinical studies with VNS [60–64]. Stimulation of norepinephrine release from the brainstem and its binding in the limbic system has been proposed as a key anti-epileptic mechanism of VNS as blockade of hippocampal α2-receptors inhibits the anti-epileptic effect of VNS in Wistar rats [61]. Of particular interest in status epilepticus may

Table 1b
Cases of non-acute or electrical forms of RSE/SRSE treated with VNS.

Author	Publication Type	Patient #	Sex	Age	Epilepsy Type	Etiology	Classification	Long-term Outcome
Morita et al., 2017	Case Report (IV)	39	M	21	Focal motor		Acute (then chronic) encephalitis with refractory, repetitive partial seizures	>50% seizure reduction
Carosella et al., 2016	Case Report (IV)	40	F	12	Focal motor	thalamic encephalomalacia with l periventricular white-matter volume loss	Electrical status epilepticus in slow-wave sleep	no ESES and seizure free
De Benedictis et al., 2013	Case Series (IV)	41	F	3	Focal myoclonic	Rasmussen encephalitis	Epilepsy partialis continua	no EPC
		42	F	10	Focal motor	Chronic encephalitis	Epilepsy partialis continua	3 EPC episodes per month
		43	F	10	Focal motor to bilateral tonic-clonic	Chronic encephalitis	Epilepsy partialis continua	short and rare EPC
		44	F	20	Focal motor	Poliodystrophy	Epilepsy partialis continua	short and rare EPC
Shen et al., 2013	Case Report (Conference Abstract) (IV)	45	M	21	Generalized (tonic-clonic) & focal myoclonic		Epilepsy partialis continua	no EPC (seizure free)

be results from one SPECT study suggesting that response to VNS may be associated with modulation of cortical $GABA_A$ receptor expression. Seizure reduction correlated with $GABA_A$ receptor density in patients after 1 year of VNS but not in matched controls [65].

Furthermore, quantitative EEG studies using different measures of synchronization suggest that VNS may acutely desynchronize the inter-ictal EEG thereby impeding the development of hypersynchronous rhythms [66]. VNS also acutely desynchronizes ictal-rhythms thereby containing seizure propagation of focal-onset seizures [67]. Electrographic seizure interruption by VNS has been demonstrated in rats and dogs [68–70] but only anecdotally in humans [15,16]. Taken together, multiple mechanisms by which VNS may contribute to cessation of RSE/SRSE are conceivable; however have yet to be proven in well controlled trials.

Limitations

The results of this systematic review must be interpreted with great caution as the analysis is limited by the inherent property of systematic reviews of ignoring potentially important differences across studies as well as by the low sample sizes and low evidence class of studies included. Additionally there was high heterogeneity in reporting of outcomes with some studies failing to report basic patient demographics such as sex or age of the patients, which of course impacts data quality. Complete documentation of all treatments before and after VNS was only available for some of the cases included in this analysis and the majority of cases failed to report electrographic outcomes.

Studying the efficacy of [adjunctive] treatments for SE is a general challenge, as it can be unclear which of the multiple treatments (or a combination thereof) has been effective or if the SE episode would have ceased without the intervention.

There is also great need for standardization of efficacy criteria in studies of RSE/SRSE and efforts have been made to evaluate the influence of different efficacy criteria on the results of observational studies on treatment of SE [71]. Redecker et al. found that "last drug introduced into the antiepileptic therapy or increased in dose within 24 h before termination of the SE without changes in the co-medication" was the most appropriate measure for the evaluation of efficacy of an AED in the treatment of SE and more reasonable than the "last antiepileptic drug (AED) administered before SE termination" [72]. Median latency from VNS implant to RSE/SRSE cessation was 8 days in this analysis and similar for KD, which is far beyond the frame of the former mentioned efficacy measure.

Duration of SE is known to represent a key predictor of outcome with mortality increasing 5-fold in patients with SE episodes lasting longer than 60 min compared to those in whom SE could be successfully treated within 30 min [73]and increased length of hospitalization representing a predictor of functional disability [74].

Considering the often long latencies to cessation of RSE/SRSE from last added therapy, it is of interest whether appropriateness of the criteria suggested by Redecker et al. may be different with non-pharmacological interventions and also vary in RSE/SRSE as opposed to SE. Furthermore, this efficacy criterion may not capture potential synergism between therapies which may be of greater importance in RSE/SRSE (e.g. hypothetical induction of GABA-A receptor expression by one therapy may be beneficial with drugs targeting GABA-A receptors; reduction of a antibodies against NMDA receptors by immunological therapies may be beneficial with drugs targeting NMDA receptors).

Randomized-controlled trials aimed at minimizing these biases can however be extremely difficult and even impossible to execute in RSE/SRSE, due patient recruitment challenges in a rare and emergency condition with heterogenous etiologies as well as for ethical reasons. Finally, this analysis contains a high fraction of case-reports which brings a high risk of reporting bias, potentially resulting in overly optimistic outcomes. Negative case-reports are less likely to be submitted for publication as there is lower interest from journals to publish them and low expectation from authors of acceptance.

The cases summarized in this systematic review are the only data currently available offering insight into acute VNS implantation in RSE/SRSE and therefore carry relevance in documenting this practiced treatment approach. Since the previous 2015 systematic review by Zeiler et al. more detailed case reports and case series have been published leading to this analysis being able to include 36% more cases. Furthermore, the previous analysis does not report on long-term outcomes, VNS settings, treatments applied prior to VNS implantation or duration of the SE episode post VNS implantation which represent important considerations. These aspects have been captured in this analysis as they are necessary to shape a prospective observation of acute implantation of VNS in RSE/SRSE, which the authors understand to be of great importance in overcoming the inherent bias of the current analysis and therefore are in the process of initiating.

Conclusion

Outcomes of our analysis are in line with those from the previous analysis suggesting that VNS has potential in interrupting RSE

Table 2
Secondary endpoints for acute cases.

Author	Patient #	SE Focal Genralized or Unclear	Convulsive/ Non-convulsive	SE Etiology	SE Treatments prior to VNS	Duration of SE prior to VNS (days)	Cessation of SE Y/N	Latency to cessation of SE (days)	mA	Hz	μsec	Duty Cycle	Long-term Outcome
Kurukumbi et al., 2019	1	G	C	Unknown encephalitis	VPA, LEV, PFL, PB	3	Y	3	1.5	30	500	16	Died 13 days after VNS implantation due to reoccurrence of SRSE
Grioni et al., 2018	2	F	C		MDZ, PFL		Y	4	1		500	10	>90% seizure reduction
	3	F	C		LEV, PB, VGB		Y		1		250	10	VNS monotherapy (no AEDs) due to minor amount of spasms only
	4	U	C		MDZ, PFL, THP		N		1		250	10	Died in palliative care
	5	F	C		Benzodiazepines (not further clarified) LEV, PB	5	Y	5	1		500	10	>90% seizure reduction
Yamazoe et al., 2017	6	F	C	anti-GluR encephalitis, fever associated	MDZ, DZP, PHY, PFL, steroid pulse, IVIG, plasma exchange	1680	Y	15	3	30	500	35	Seizure-free
Pichon et al., 2016	7	U - G?	C										Seizure-free
	8	U -G?	C										50% seizure reduction
	9	U - G?	C										Seizure-free
Yazdi et al., 2016	10	F	NC	evacuation of a right-sided spontaneous subdural hematoma fever associated	MDZ, PHY, VPA, LEV, PB, PFL	14	Y	2	1.5	30	500	29	
Alsaadi et al., 2015	11	F	NC	anti-NMDA encephalitis	MDZ, PHY, VPA, LEV, PB, acyclovir	110	Y	7	2.5				seizure-free
Hoang et al., 2014	12	F	NC	Fever associated	LSM, TPM, DZP, PB, Ketogenic diet, high-dosed steroids, IVIG, plasmapheresis								Perampanel initated 3.5 months after admission leading to RSE cessation
Donahue et al., 2013	13	G					Y	7					
	14	G					Y	7					
	15	G					N	21					
	16	G					N						
	17	G					N	84					
Howell et al., 2012	18	G		FIRES			N		1.75			58	Treatment withdrawal and death on day 29
Lin and Ko 2012	19	U-G		anti-NMDA encephalitis	PB, PFL, Ketogenic diet, KET	“weeks"	Y	14					
	20	U-G		unknown encephalitis	PB, PFL, Ketogenic diet, KET	“months"	Y	14					
Soto et al., 2012	21	U	C	Fever associated	PB		Y		1	30	500	10	free of GTCS
Shatzmiller et al., 2011	22	G	NC	anti-NMDA encephalitis	PB, PFL, KET, IVIG, antibiotics, acyclovir, steroids		N						patient improved 1 after four pulses of cylcophosphamide (after VNS)
O'Neill et al., 2011	23	G	C		PB, PFL, KET	21	Y	9	1				>75% seizure-reduction
Soto et al., 2009	24	U	C				Y		1	30	500	10	free of GTCS
Thielemann et al., 2009	25	G	C	AED withdrawal	MDZ, VPA, LEV, PB, PFL, KET	25	Y	8	1		250	35	improvement beyond pre-hospital baseline (1 nocturnal seizure per week vs multiple daily before)
De Herdt et al., 2009	26	G	NC		MDZ, LRZ, PB, THP, PFL	11	Y	30	1.75			10	Seizure-free

(*continued on next page*)

Table 2 (*continued*)

Author	Patient #	SE Focal Genralized or Unclear	Convulsive/ Non-convulsive	SE Etiology	SE Treatments prior to VNS	Duration of SE prior to VNS (days)	Cessation of SE Y/N	Latency to cessation of SE (days)	mA	Hz	µsec	Duty Cycle	Long-term Outcome
Zamponi et al., 2008	27	G					Y	"early cessation"					
	28	G					Y	"early cessation"					
	29	G					Y	"early cessation"					
Patwardhan et al., 2005	30	G	C	AED withdrawal	PHY, VPA, PB	12	Y	18	1	20	250	16	Seizure-free
Zimmerman et al., 2005	31	U		AED withdrawal	LRZ, PHY, VPA, PB	7	Y	3	3	30	500	51	
	32	U		AED withdrawal	LRZ, PHY, VPA, PB		Y		3	30	500	51	died from GTCS 1 year later
	33	U		AED withdrawal	LRZ, PHY, VPA, PB	35	Y	5	3	30	500	51	
Malik et al., 2005	34	G	C										significant seizure reduction
	35	G	C										significant seizure reduction
	36	G											no seizure reduction
Skaff et al., 2001	37	G	C	Human papiloma virus B19	LRZ, PHY, THP, acyclovir	>52 days	Y						(not clear in w hich order TPM, LRZ and VNS were given after 52 days
Winston et al., 2001	38	G	C	Fever-associated	MDZ, LRZ, VPA	15	Y	12	2				>50% seizure reduction

MDZ = midazolam; PFL = propofol; LEV = levetiracetam; PB = phenobarbital; VGB = vigabatrin; DZP = diazepam; PHY = phenytoin; VPA = valproic acid; LSM = lacosamide; TPM = topiramate; KET = ketamine; LRZ = lorazepam; THP = thiopental.

and SRSE in many patients with an overall response rate of 74%. Data quality however is low (level IV) and the risk for reporting bias is high. Further prospective studies are warranted to investigate the role of acute VNS in RSE and SRSE and should elucidate optimal stimulation paradigms, timing of the acute implantation and potential synergies with pharmacological agents.

Disclosures

Maxine Dibué-Adjei is an employee of LivaNova Deutschland GmbH – a fully-owned subsidiary of LivaNova PLC – and holds stock options.

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