Brain Stimulation 12 (2019) 835–844

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Neuromodulation techniques for status epilepticus: A review

Daniel San-juan [a, *], Daniel Oswaldo Dávila-Rodríguez [a], Christian Ramos Jiménez [b], Manuel Sánchez González [c], Sergio Mayorquín Carranza [d], Jesús Ricardo Hernández Mendoza [e], David J. Anschel [f]

[a] Neurophysiology Department, National Institute of Neurology and Neurosurgery Manuel Velasco Suárez, Mexico City, Mexico
[b] Faculty of Medicine, Autonomous University of State of Mexico, Toluca de Lerdo, State of Mexico, Mexico
[c] Faculty of Medicine, University of Guadalajara, Guadalajara, Jalisco, Mexico
[d] Academic Unit of Medicine, Autonomous University of Nayarit, Tepic, Nayarit, Mexico
[e] Faculty of Medicine Mexicali, Autonomous University of Baja California, Dr. Humberto Torres Sangines, Mexicali, Baja California, Mexico
[f] Comprehensive Epilepsy Center of Long Island, Port Jefferson, NY, USA

ARTICLE INFO

Article history:
Received 21 August 2018
Received in revised form
5 April 2019
Accepted 14 April 2019
Available online 21 April 2019

Keywords:
Electroconvulsive therapy
Vagal nerve stimulation
Transcranial magnetic stimulation
Deep brain stimulation
Status epilepticus
Refractory status epilepticus

ABSTRACT

Background: Electroconvulsive therapy (ECT), Vagal Nerve Stimulation (VNS), Transcranial Magnetic Stimulation (TMS) and Deep Brain Stimulation (DBS) are neuromodulation therapies that have been used to treat Status Epilepticus (SE).
Objective: Review the literature about the efficacy and safety of neuromodulation therapies in SE in humans.
Methods: We searched studies in PubMed, Scopus, Google Scholar and Science Direct (inception to June 2018). Four review authors independently selected the studies, extracted data and assessed the methodological quality of the studies using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, PRISMA guidelines, Oxford and GRADE scales, and Murad et al., 2018 methodological quality and synthesis of case series and case reports.
Results: We 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 and DBS aborted SE, however, 50% of patients with DBS had severe adverse events.
Conclusions: 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 studies on the relationship be-tween efficacy and safety.

Introduction

Status epilepticus (SE) is a life-threatening neurologic emergency with an incidence from 10 to 41 per 100,000 per year [1,2]. The mortality of SE is 20%–50%. with acute symptomatic SE carrying a greater risk than chronic SE [1,3–5]. Refractory SE (RSE) and Super-Refractory SE (SRSE), occur in 29–43% and 12–26% of SE cases respectively.

According to the International League Against Epilepsy status epilepticus is defined as a "*condition resulting from a deficiency of the mechanisms responsible for the cessation of the crisis or the beginning of mechanisms that lead to abnormally prolonged seizures* (>30min)" [6].

Refractory SE refers to recurrent seizure activity despite the use of two antiepileptic drugs (appropriately chosen and administered at correct doses), one of which must be from the benzodiazepine group [7]. Super-Refractory SE, persists for ≥24 h after starting treatment with anesthetics or that has recurred despite the use of general anesthesia; it also applies to those situations in which SE recurs upon reduction of anesthesia [8].

The treatment of the SE has 3 main objectives: (1) control seizures to prevent initial excitotoxicity, (2) neuroprotection and (3) avoid or treat those complications due to loss of consciousness and the use of anesthetics [9]. Multiple immunomodulation drugs and non-pharmacological therapies have been used in the treatment of

* Corresponding author. Clinical Research Department, National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877, La Fama, Tlalpan, Mexico City, 14269, Mexico.
E-mail address: dirinvest@innn.edu.mx (D. San-juan).

https://doi.org/10.1016/j.brs.2019.04.005
1935-861X/

RSE, including neuromodulation techniques [9]. Neuromodulation techniques may abort seizures by: releasing inhibitory neurotransmitters and/or electrically inhibiting the neurons surrounding the seizure focus [10]. The neuromodulation therapies that have been used to treat patient with SE are electroconvulsive therapy (ECT), implanted direct vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). Case reports and series [9] show promising results. A systematic review that analyzes these neuromodulation techniques has not been carried out; the present report aims to evaluate the efficacy of these interventions.

Materials and methods

The review was executed according to the recommendations of the Cochrane Handbook for Systematic Reviews of interventions [11], and the present document follows PRISMA (Preferred Reporting Reviews and MetaAnalyses) guidelines [12].

Our operational definitions of SE: Generalized, tonic-clonic convulsive SE in adults and older children (>5 years old) refers to >5 min of (a) continuous seizures or (b) two or more discrete seizures between which there is an incomplete recovery of consciousness. We deemed a therapy as effective when it resulted in cessation of epileptic activity in the electroencephalogram or clinical seizures.

Literature search

We searched for articles in PubMed, Scopus, Google scholar and Science Direct through June 2018 using the keywords 'VNS' or 'vagal nerve stimulation' or 'vagus nerve stimulation' or 'transcranial magnetic stimulation' or 'TMS' or 'electroconvulsive therapy' or 'ECT' or 'deep brain stimulation' or 'DBS' or 'status epilepticus' or 'SE' or 'refractory status epilepticus' or 'RSE' or 'super refractory status epilepticus' and 'SRSE' and human.

Selection criteria

The following criteria were adopted: (1) articles written in English, (2) original articles and case reports. We excluded the following: (1) review articles; (2) articles reporting duplicate data or data extracted from original articles; (3) abstracts; (4) articles alluding to epilepsy or multidrug resistant epilepsy without SE.

Data extraction

For each study, four authors extracted data independently (C.R.J., S.M.C., M.S.G. and J.R.H.M.) and one checked data extraction (D.S.). The reviewers decided if all titles and abstracts of the articles met the inclusion criteria for this study. All chosen articles were assessed by their full text to confirm they met the inclusion criteria. Discrepancies were resolved by consensus with the main author (D.S.).

An electronic database was used to collect and store all data from selected articles. We developed a structured checklist to extract the following variables: (1) Demographics and clinical characteristics, age, etiology of the seizures and current antiepileptic medication (2) Neuromodulation treatment parameters, which included electrodes and device positioning, current, charge, duration and sessions of the therapy (3) Therapy outcomes and associated adverse effects.

Quality assessment

According to Oxford criteria, the Grading Recommendation Assessment Development and Education (GRADE) criteria and the methodology of Murad [13,14,15], we decided to use two reviewers who independently assessed the level of evidence for each included study and address the following issues that influence the quality of data: (1) selective outcome reporting whether the SE was aborted or not (aborted was defined as the cessation of the epileptic activity or seizure); (2) follow-up after neuromodulation therapy and (3) the neuromodulation parameters used in each therapy.

Using those techniques, we addressed the following issues that influence the quality of data and assessed the following variables: (1) selective outcome reporting whether the SE was aborted or not; (2) follow-up after neuromodulation therapy and (3) the neuromodulation parameters used in each therapy.

Quantitative analysis

Analysis was performed using Excel and results reported with descriptive statistics due to the size and number of studies. We did not elaborate on meta-analysis due to statistical heterogeneity of included studies.

Results

We found 27 research articles that met criteria. The flowchart of this process is shown in Fig. 1. In the next sections, we describe each neuromodulation therapy used in SE. Table 1 summarizes each neuromodulation technique.

Electroconvulsive therapy

We included 10 articles with 20 SE patients. The main etiology of SE was viral encephalitis, the usual electrodes location was bifronto-temporal; the ECT regime was divided in series and sessions for each patient with an average initial load and amperage of 504 mC and 800 mA[16, 17]. All patients were being treated with multiple antiepileptic drugs (AEDs). Two (5%) patients developed memory impairment [18]. The SE was aborted in 16/20 (80%); 3/4 of non-responders were in the same study, treatment consisted of a 504-mC ($\approx$99.4 J) stimulus with a constant 0.5-millisecond pulse width during 3–7 sessions [18].

Invasive vagal nerve stimulation

We analyzed 9 articles describing the use of VNS applied in 16 patients with SE, with a range of age from 7 to 67 years-old. Etiologies of SE were heterogeneous, the initial VNS parameters were set to 0.25 mA, 500 μs, 30 Hz, 30s on/5 min off and then adjusted to different parameters up to 3.00 mA [19]. All patients were treated with multiple AEDs. Two studies reported adverse effects; one patient had an acute episode of asystole [20] and one patient developed dysphonia, mild cough and bradycardia [21]. SE resolved in 15/16 (93.7%) patients [19–22].

Transcranial magnetic stimulation

For TMS we included 4 articles with 5 SE patients of which 4 had an unknown etiology and one had an ischemic-hypoxic encephalopathy post-cardiopulmonary resuscitation. The usual stimulation regions were Cz and temporal regions. The TMS regime was divided in sessions for each patient with trains of 0.5–1 Hz with different stimulation times for each patient [23,24]. All patients had multiple AEDs [23–26]. The SE was aborted in all patients and there were no adverse effects in any of the cases [23–26].

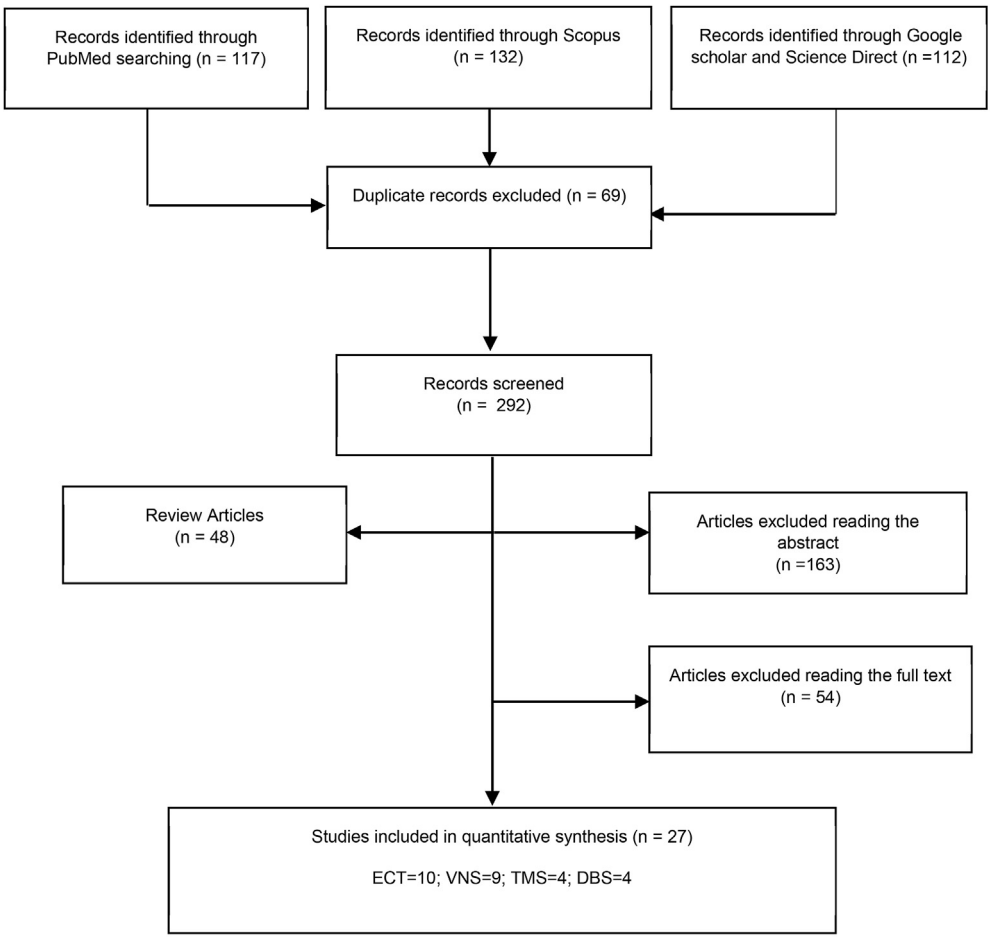

Fig. 1. Flowchart of the selection of the studies for this review.

Deep brain stimulation

We included 4 articles with 4 SE patients. The DBS electrodes were positioned in the thalamus and subthalamus regions with different patterns of stimulation. All patients had multiple AEDs and other drugs included in their therapies [27–30]. Two (50%) patients developed adverse effects (contralateral upper limb paresthesia and infection of the electrodes) [27,28]. SE was terminated in all 4 patients [27–30]; however, one was diagnosed with SRSE and, the DBS was implemented together with continuous ketamine infusion [30]. In these relatively young (<30 yo) patients DBS was used successfully as a therapeutic tool of last resort [27–30] (Table 1).

Level of evidence for neuromodulation therapies

Based on two independent reviewers, 27 studies were included in this review and all were classified as GRADE D evidence and Oxford level 4. In addition, according to Murad's methodology all the studies obtained at least 7 out of 8.

Discussion

The exact mechanisms underlying the development of SE refractoriness are incompletely understood. Evidence has accumulated that impairment of gamma-aminobutyric acid (GABA)–mediated inhibition related to internalization of GABA receptors and upregulation of excitatory AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and NMDA (N-methyl-d-aspartate) receptors may play a role in the development of increasing refractoriness to treatment [43].

Currently, VNS, DBS and responsive cortical stimulation (Neuropace©) are FDA approved to treat refractory focal epilepsies with similar efficacy [44], yet only 5–23% of patients achieve seizure-free periods. The mechanisms of action of neurostimulation differ depending on targets and stimulation parameters used and are incompletely understood [45]. Below we discuss the different neuromodulation techniques applied in patients with SE.

Electroconvulsive therapy

Electroconvulsive therapy is a technique that non-invasively stimulates the brain electrically to cause a seizureand is carried out under sedation [9,46]. The first studies on ECT reported to treat epilepsy were conducted by Kalinowsky and Caplan in the 1940s [47,48]. Viparelli et al. was the first to describe the use of ECT in a patient with RSE [49]. In his study, he reported a decrease in epileptic seizures when using ECT with a patient after treatment with phenytoin and diazepam failed [49].

The mechanism of action is not known. It has been hypothesized that ECT generates alterations in neurotransmitters levels, including increasing GABA, which creates an inhibition of the action potential [50]. Another mechanism that has been proposed relates to an elevation in seizure threshold post intervention in patients with severe mood disorders [51–54]. Animal studies indicate this may be due to the effect of an endogenous opiod. In some studies, it has been shown that in patients with severe mood

Table 1
Summary of neuromodulation therapies.

Reference	No. patients	Age (years)	Seizures' etiology	Electrodes location/ Stimulated region/Device	Treatment regime	Load (mC)	Amperage (mA)	Current drugs AEDs	Adverse effects	SE aborted and Latency from stimulation to SE abortion	Duration of SE before therapy	Setting
Electroconvulsive therapy (ECT)												
(Carrasco González, Palomar and Rovira, 1997) ([31])	1	25	Post-traumatic changes in the right frontal and left temporal lobes	?	6 sessions (3/week)	?	?	PHT, PB, CBZ, DZP	?	Yes, 1 month	40 days	?
(Griesemer et al., 1997) ([32])	2	13	Microgyria	?	4 total series: week 1: 4 sessions over 9d; week 52: 3 sessions over 3d; week 82: 3 daily sessions over 2d; week 84: 3 sessions in 1d	22-403*	?	PHT, VPA, PB, CZP, LTG, GBP, FBM, ACZ	Lethargy, mild head drops	Yes, 590 days	1 month	?
		10	Generalized tonic-clonic seizures	?	3 total series: week 1: 3 sessions over 5d; week 3: 3 sessions over 2d; week 5: 3 sessions over 2d	22-576*	?	PHT, VPA, PB, CBZ, GBP, LZP, FBM	?	Yes, 39 days	18 weeks	?
(Lisanby et al., 2001) ([33])	1	36	Bifrontal cortical dysplasia: Complex partial epilepsy with and without secondary generalization and atonic drop attacks	Right frontotemporal and left parietal	5 total series: 1. 4 sessions in 1d; 2. 2 sessions in 1d; 3. 1 session in 1d; 4. 1 session in 1d; 5. 1 session in 1d	576-3379*	800	PHT, PB, VGB, MDL, NTZ and PTB	?	Yes, 1 month	26 days	NICU
(Cline and Roos, 2007) [16]	1	39	Viral encephalitis	Bifronto-temporal	3 total series: 1. 3 sessions in 1 d; 2. 3 sessions in 1d; 3. 3 sessions in 1d (consecutive days)	576	800	VPA, TPM, OXC, LZP, FBM, LEV, FPHT and PTB	?	Yes, 51 days	103 days	ED
(Kamel et al., 2010) [17]	3	32	Viral encephalitis	Bifronto-temporal	4 total series: 1. 3 sessions in 1d; 2. 4 sessions in 1 d; 3. 3 sessions in 1d; 4. 3 sessions in 1d (two days after third session)	504.6–510.2*	900–910	PHT, VPA. PB, LEV, TPM, PTB and KET	Retrograde amnesia for the months prior to her illness and anterograde amnesia for the duration of her stay in the ICU	Yes, 4 days	30 days	ICU
		41	Viral encephalitis	Bifronto-temporal				VPA, LEV, FPHT, PTB and KET.	–	No,	30 days	ICU
		26	Viral encephalitis	Bifronto-temporal	2 cycles of 4 series: 1. 3 sessions in 1d; 2. 4 sessions in 1 d; 3. 3 sessions in 1d; 4. 3 sessions in 1d (two days after third session)			PHT, VPA, PB, TPM, LEV, PTB, ISO and KET.	Mild difficulty with short-term memory and concentration	Yes, 20 days	70 days	ICU
(Shin et al., 2011) ([34])	1	7	Intractable epilepsy (refractory epilepsy)	Bitemporal	2 cycles of 2 series: 1. 3 sessions in 1d; 2. 3 sessions in 1d (5 days apart between cycle)	?	800	VPA, TPM, LEV, CLB, MDL, PTB and KET.	?	Yes, 9 days	14 days	EMU
(Mirás et al., 2016) ([35])	1	4	Febrile Infection-Related Epilepsy Syndrome	Bifronto-temporal	14 sessions in 5 different days over 12 days	?	?	PHT, VPA, LEV, MDL, TPM, LCM, TP and KET.	?	Yes, 12 days	56 days	ICU

(Ahmed et al., 2017) [18]	8	?	?	Bifronto-temporal	3 sessions daily (consecutive)	504	?	PHT, VPA, PB, CZP, LCM, LEV, LZP, TPM, PTB, PROP, MP, RFM, and fludrocortisone.	?	Yes, 3 days	36 days	?
		?	?	Bifronto-temporal	4 sessions (3 consecutive, 2 days off, 1)	505	?	VPA, LTG, MDL,PB, TPM, FEN, FPHT, PTB and DEXA.	?	Yes, 6 days	7 days	?
		?	History of seizure disorder	Bifronto-temporal	3 sessions daily (consecutive)	506	?	VPA, CLB, CZP, FBM, LZP, LCM, LEV, MDL, PB, TPM, FPHT, PTB and PROP.	?	Yes, 3 days	18 days	?
		?	Subdural hematoma	Bifronto-temporal	4 sessions (3 consecutive, 2 days off, 1)	507	?	VPA, PB, LEV, LCM, LTG, LZP, TPM, PTB, DEXA and HCT.	?	Yes, 6 days	19 days	?
		?	Encephalitis from inmunization	Bifronto-temporal	6 sessions (2 consecutive, 4 days off, 2 every other day, 2 off, 2 every other day)	508	?	VPA, PB, LEV, DZP, LZP, TPM, PTB, PROP and HCT.	?	Yes	3 days	?
		?	?	Bifronto-temporal	7 sessions (3 every other day, 2 off, 4 consecutive)	509	?	VPA, PB, LEV, FBM, LCM, MDL, PHT, TPM, KET and PROP.	?	No	26 days	?
		?	Cerebrovascular accident 2 months prior	Bifronto-temporal	3 sessions daily (consecutive)	510	?	LCM, LEV, MDL, TPM, FPHT, PTB and PER.	?	No	24 days	?
		?	?	Bifronto-temporal	6 sessions (3 consecutive, 4 days off, 3 consecutive)	511	?	LCM, LEV, LZP, PB, VPA, FPHT, PTB, PROP, MP and HCT.	?	No	9 days	?
(Pinchotti, Abbot and Quinn, 2018) ([36])	1	51	Severe alcohol use disorder	Bitemporal and bifronto-parietal	3 total series: 1. 6 sessions in 1d (bitemporal); 2. 3 sessions in 1 day (bitemporal); 3. 2 sessions in 1d (bifrontoparietal) [consecutive days]	504	900	LCM, LEV, PHT, MDL, LZP, VPA, TPM, PB, ZNS, CBZ, PTB, KET, MP, ALLO and PER.	Spontaneous eye opening.	Yes,	?	?
(Chan et al., 2018) ([37])	1	31	Acute infectious meingoencephalitis		3 total series: 1. 3 sessions in 1d; 2. 3 sessions in 1d; 3. 3 sessions in 1 d.	?	800	PHT, VPA, MDL, PROP, PB, LEV, TP and KET.	Cognitive decline and personality changes.	Yes	?	?
Vagal Nerve Stimulation (VNS)												
(Winston et al., 2001) ([38])	1	13	Primary generalized epilepsy	Left vagus nerve	0.25 mA, 250 us, 25 Hz 7s on/120 s off	?	0.25 up to 1.75	VPA, FBM, TPM, DZP, LZP	?	Yes, 1 day	9 days	ICU
(Patwardhan et al., 2005) ([39])	1	30	Primary generalized epilepsy	Left vagus nerve	0.25 mA, 250 μs, 20 Hz, 30 s 0n/5 min off	?	0.25 up to 1.0	PHT, VPA, CBZ, TPM, PB, TGB, LEV, GBP, MDL, PTB, PROP	?	Yes, 1 day	12 days	RU
(De Herdt et al., 2009) [22]	1	7	Thrombosis right internal cerebral vein/Right thalamic bleeding	Left vagus nerve	0.25 mA, 500 μs, 30 Hz, 30s on/5 min off	?	0.25 up to 1.75	PHT, VPA, PB, LTG, CZP, LZP, MDL, TPM, ESM, PROP, TP,	Bradycardia, Acute episode of asystole	Yes, 3 days	11 days	ICU
(Carreño et al., 2010) ([40])	1	29	Autosomal dominant nocturnal frontal lobe epilepsy	Left vagus nerve	0.25 mA, 500 μs, 30 Hz, 30s on/5 min off every two weeks	?	0.25 up to 1.5 and 2	PHT, VPA, PB, CBZ, TPM, LTG, ESM, CLB, VGB, GBP, CZP, LEV,	?	Yes, 3 months	?	?

(*continued on next page*)

Table 1 (*continued*)

Reference	No. patients	Age (years)	Seizures' etiology	Electrodes location/ Stimulated region/Device	Treatment regime	Load (mC)	Amperage (mA)	Current drugs AEDs	Adverse effects	SE aborted and Latency from stimulation to SE abortion	Duration of SE before therapy	Setting
(O'Neill et al., 2011) ([41])	1	23	Primary generalized epilepsy precipitated by ladder fall	Left vagus nerve	1.0 mA, 250 μs, 25 Hz, 7s on/0.3 min off	?	?	VPA, TPM, LTG, MDL, LEV, PROP, PTB and KET.	?	Yes, 10 days	3 weeks	RU
(Sierra-Marcos et al., 2012) [21]	8	25.1 (14–40)	2 ADNFLE 2 Right frontal criptogenic epilepsy, 4 Multifocal symptomatic epilepsy	Left vagus nerve	0.25 mA, 500 μs, 30 Hz, 30s on/5 min off	?	1.7 mA (0.75 and 2.25 mA)	12 AEDs not specified	3/8 patients had moderate or mild coughing and dysphonia	5/8, Yes, ?	?	?
(Yazdi and Schumaker, 2016) [22]	1	67	Spontaneous right-sided subdural hematoma	Left vagus nerve	1.5 mA, 500 μs, 30 Hz, 14s on/0.8 m off	?	1.5 up to 2	PHT, VPA, PB, MDL, LEV, CBZ, PROP and DEXA.	?	Yes, 2 weeks	5 days	ICU
(Yamazoe et al., 2017) [19]	1	24	Anti-GluR encephalitis.	Left vagus nerve	3 mA and 35% duty cycle	?	3	PHT, VPA, TPM, MDL, DZP, LTG, LEV, ZNS	?	Yes, 2 months	14 months	ICU
(Arhan et al., no date) ([42])	1	13	HSV 1 encephalitis	Left vagus nerve	0.25 mA, 250 us, 30 Hz, 30s on/5 min off	?	0.25 up 2	CBZ, LEV, CLB, PHT, DZP, MDL.	At 2.0 mA - Secondary generalized clonic seizures on the left side of her face and SE	No, stopped after lowering voltage	1 day	EMU
Transcranial Magnetic Stimulation (TMS)												
(Thordstein and Constantinescu, 2012a) [25]	1	68	Unknown etiology	The right angle to the right central sulcus, right temporo-occipital region, left fronto-anterior	Stimuli were delivered at 0.5 Hz over 60 min each session for 8 days.	?	?	CBZ, DZP, PROP, VPA, MDL, PHT, TPM, and LEV	No adverse effects	Yes, 8 days	44 days	ICU
(Liu et al., 2013b) [23]	2	46	Unknown etiology, intractable epilepsy since childhood	Right centrotemporal region c4/t4	Unique session, A single train at 1 Hz applied for 20 min	?	?	PB, PGB, LTG, FPHT, LCM, LEV, MDL and PROP	No adverse effects	Yes, Single session	21 days	ICU
		51	Unknown etiology Seizures originated from the left mid and posterior temporal region	left sensorimotor cortex	Unique session, A single train at 1 Hz applied for 30 min	?	?	LTG, LEV, FBM, LZP, LCM	No adverse effects	Yes, Single session	9 days	ICU
(Van-Haerents et al., 2015) [24]	1	24	At age 22, his first generalized convulsive seizure, EEG monitoring, seizures arise from either the left or right occipital pole	left occipital focus with the coil center to O1 and the handle pointed to T5	11 Sessions over ten days (two sessions the first day, then 1 session every day) each session consisting of three 10-min trains of 1 Hz pulses at 95–100% resting MT (1 min between trains; 1800 pulses per session	?	?	ZNS, LTG, PB and PHT	No adverse effects	Yes, 10 days	5 months	Neurology floor
(Naro et al., 2015) [26]	1	35	postanoxic brain injury following a cardiac arrest.	standard round coil over the vertex (Cz)	Unique session train of 1 Hz 1200 pulses (four trains of 300 stimuli,	?	?	LEV, VPA, LZP	No adverse effects	Yes, Single session	7 days	Neurology floor

				30 s of intertrain interval) at 50% of the maximumo output							
Deep Brain Stimulation (DBS)											
(Franzini et al., 2008) [27]	1	22	Rasmussen encephalitis	Left caudal zona incerta	Monopolar with contacts 1 and 2 as cathodes, 90 μs, 100 Hz	?	2	BZD, AZT, IgM IV, CCS	Contralateral upper limb paresthesia	Yes, Immediately after stimulation	–	OR
(Valentín et al., 2012) [28]	1	27	Anoxic injury	Bilateral centromedian thalamic nuclei	6 Hz, 90 μs	?	5	PHT, LEV, LZP, PROP, VPA TPM, PB, MDL, sodium TP, IVIG, MP	Infection of the electrodes	Yes, Immediately after stimulation	5 weeks	OR
(Lee et al., 2017) [29]	1	17	Progressive seizure activity	Bilateral anterior thalamic nucleus	Continuous bilateral stimulation, 145 Hz, and 90 microseconds (increase to 120 microseconds after 3 days)	?	8	LTG, CLB, TPM, LEV, LZP, VPA, PER, MDL	No adverse effects	Yes, Immediately after stimulation	4 weeks	OR
(Lehtimäki et al., 2017) [30]	1	17	CVID (Common Variable Immunodeficiency) associated encephalomyelitis	Centromedian nucleus of the thalamus	180 Hz, 150μs	?	7	BZD, PHT, PROP, TP, MDL, racemic KET, S-KET, LEV, TPM, LCM, LZP, CLB, CCS, IVIG	No adverse effects	Yes, Two weeks	59 days	ICU

AEDs, Anti-epileptic drugs. ACZ, Acetazolamide; ALLO, Allopregnanolone; AZT, Azathioprine; BZD, Benzodiazepine; CBZ, Carbamazepine; CCS, Corticosteroids; CLB, Clobazam; CZP, Clonazepam; DEXA, Dexamethasone; DZP, Diazepam; ESM, Ethosuximide; FBM, Felbamate; FEN, Fentanyl; FPHT, Fosphenytoin; GBP, Gabapentin; HCT, Hydrocortisone; IgM IV, Immunoglobulin M intravenous; ISO, Isoflurane; IVIG, Intravenous immunoglobulin; KET, Ketamine; LCM, Lacosamide; LEV, Levetiracetam; LTG, Lamotrigine; LZP, Lorazepam; MDL, Midazolam; MP, Methylprednisone; NTZ, Nitrazepam; OXC, Oxcarbazepine; PB, Phenobarbital; PER, Perampanel; PGB, Pregabalin; PHT, Phenytoin; PROP, Propofol; PTB, Pentobarbital; PTR, Pheneturide; RFM, Rufinamide; TGB, Tiagabine; TP, Thiopental; TPM, Topiramate; VGB, Vigabatrin; VPA, Valproic acid; ZNS, Zonisamid, ? = Unknown. *Minimum and maximum range of charge between ECT sessions.

disorders the epileptic thresholds were increased in 21% of patients with ECT [51]. The mechanism of ETC has also been postulated to involve changes in prolactin levels [55]. A possibility which is non-exclusive of the above mechanisms involves the concept that in some cases status epilepticus, may actually be “status hypo-epilepticus.” In this concept the seizures persist, because endogenous mechanisms of seizure termination have failed. The induction of a “more complete” seizure by ECT serves to more effectively initiate the endogenous seizure termination mechanism(s).

In a review of ECT in RSE, 11 cases were reported to demonstrate safety and efficacy [47]. Likewise, a systematic review suggests ECT is an effective treatment for RSE, but this review does not recommend it as a routine technique for treating SE, because all retrospective heterogeneous studies were an Oxford level 4, GRADE D level of evidence with a potential for publication bias [56]. In our review, we found an 80% rate of disruption of SE and 5% risk of adverse events.

Vagal nerve stimulation

This invasive technique consists of an electrical generator implanted in the chest wall, and a lead wire tunneled rostral to the vagus nerve. The electrode delivers intermittent stimulation with set parameters, including output current, frequency, pulse width, and stimulation on/off time [57]. To reduce cardiac complications it is implanted on the left vagus nerve [58].

The effectiveness of VNS may be related to activation of unmyelinated C fibers, or an increase of bilateral thalamic blood flow and a secondary increase of inhibitory neurotransmitters [57,59]. Human studies have demonstrated an increase in CSF GABA levels [60]. Animal studies have indicated an increase in noradrenergic secretion via the locus ceruleus and serotonergic transmission via the raphe magnus with VNS that may lead to seizure inhibition [61]. Possibleadverse effects include pharyngeal dysesthesias, dysphonia, cough, and cardiac arrhythmia [22,62].

The earliest attempts at VNS to treat epilepsy was using a transcutaneous stimulator in 1880 [63]; Studies demonstrating changes in the EEG patterns after VNS were made in the 1930s [64,65] and it was used in humans for the first time for refractory epilepsy in 1988. In 1997 VNS was approved by the FDA for adjunctive treatment to reduce seizure frequency for medically refractory epilepsy in patients older than 12 years (Cyberonics/LivaNova, Clear Lake, Texas). Vagal nerve stimulation has been widely used for the treatment for epilepsy, overall reducing seizure frequency by ~50% with 2–6% of patient having seizure freedom [57].

Although Zeiler et al. [66] reported 76% cessation of RSE with VNS insertion, we can not strongly recommend its implantation with low scores on the Oxford and GRADE scales. We found that VNS was applied to SE of different etiologies and limited ages with a 93.7% rate of resolution of SE with adverse events ranging from dysphonia to asystole. We are cautiously optimistic about the future role of VNS in RSE, including optimization of dosing based on etiology and other patient specific factors.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique providing cortical stimulation, based on the principles of electromagnetic induction [67]. The electric field generated is of sufficient magnitude to depolarize neurons [69]. A repetitive train of TMS can cause a lasting change in neuronal activity [70].

The first published studies of the effects of rTMS on the motor cortex described the fact that a high frequency rTMS (over 5 Hz) can saturate the inhibitory capacity of the cortical network producing an increase in excitability [71,72]. Cortical excitability may be

reduced with a low frequency train (<1 Hz) of rTMS and increased with a high frequency train (>10 Hz) rTMS [73]. It has been proposed that the long-term effects in terms of seizure reduction are related to a reduction in cortical excitability after long-term potentiation or depression [74]. rTMS has induced long-term cortical excitability changes in the treatment of several neuronal/psychiatric diseases, such as personality disorders, Parkinson's and epilepsy [67]. Animal models in epilepsy have demostrated the antiepileptic effect of rTMS [75,76]. In humans, a systematic review of rTMS for refractory epilepsy suggests it is safe and tolerable with improvement in seizure frequency in the majority of studies [77]. Recent evidence-based guidelines support level C evidence for rTMS in the treatment of epilepsy [78].

Patients with epilepsy tolerate rTMS well, without reports of exacerbation of seizures [74,79]. The most common side effects of rTMS in adults include headache and scalp pain [68,80].

The number of published patients with SE treated with TMS is very small, however all of the patients who underwent TMS aborted the SE without adverse effects [21,22,26,80]. Like other neuromodulation techniques prospectively designed studies will expand upon these preliminary findings.

Deep brain stimulation

DBS consists of stereotactic neurosurgical implantation of stimulating electrodes into deep brain structures. DBS uses a device with three implantable components: quadripolar brain leads (contain a group of four electrodes on its distal end), neurostimulators, and extension wires. After the lead implantation the neurostimulator is typically placed in the chest wall [82]. The efficacy and safety of deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) for epilepsy has been demonstrated by a randomized trial [83].

Despite the increasing interest in neuromodulation for epilepsy, the mechanism of action of DBS is still poorly understood. Complex functional effects of chronic DBS on neural pathways have been proposed including long term plasticity effects through changes in gene and protein expression [84].

Based on our review it appears that there are cases where this therapy is useful in the treatment of SE, even RSE and SRSE. Targets have included: left caudal zona incerta (Czi), bilateral centromedian thalamic nuclei (CMN), bilateral anterior thalamic nucleus (ATN). Other proposed brain regions for stimulation include cerebellum, centromedian nucleus of the thalamus, caudate nucleus, subthalamic nucleus, hippocampus and nucleus accumbens [83]. New DBS targets are continuously being identified and characterized for patients with difficult to treat epilepsy [83]. Fifty percente of patients in SE had severe adverse effects related to the electrodes or stimulation protocol.

In our opinion the use of the neuromodulation techniques for the treatment of SE based on retrospective studies show high efficacy, however, due to the different methodology and poor study design of the published articles, our conclusions need to be considered with caution. Additionally, we suspect that publication bias is likely accounting for some of the purported efficacy of these techniques. It is unknown which neuromodulation therapy and parameters may be most appropriate based on patient specific factors such as etiology or type of SE, additionally to the specific technical requirements and costs of each treatment.

Limitations

The impact of gray literature and unpublished studies on the conclusions of systematic reviews and meta-analyses has not been comprehensively clarified [85]. We addressed this issue in our chosen inclusion and exclusion criteria. Overall the results are favorable using neuromodulation in the treatment of status epilepticus, but there is no data suggesting one modality is superior to another. Additionally, patient selection and specific protocols are not established.

Finally, in this systematic review we only analyzed retrospective studies, despite their associated limitations we feel that preliminary data supports further exploration using prospective studies.

Conclusions

Case series and reports suggest that neuromodulation therapies can abort SE in >80% of patients (Oxford scale and GRADE were level 4 and D) with a variety of adverse effects. Further prospective studies are required for these therapies to determine their efficacy and safety.

Declaration of interests

None.

Acknowledgments

C. R. J., M. S. G., S. M. C. and J. R. H. M. receive founding by “Programa Delfín” and D.O.D.R. receive founding by the Armstrong Foundation.

References

[1] Logroscino G, Hesdorffer DC, Cascino G, Hauser WA, Coeytaux A, Galobardes B. Mortality after a first episode of status epilepticus in the United States and Europe. Epilepsia 2005;46:46–8. https://doi.org/10.1111/j.1528-1167.2005.00409.x.
[2] Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006;5:246–56. https://doi.org/10.1016/S1474-4422(06)70374-X.
[3] Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. Neurology 1997;58:537–41. https://doi.org/10.1212/WNL.58.4.537.
[4] Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus-related hospitalizations and mortality: redefined in US practice over time. JAMA Neurol 2015;72:650–5. https://doi.org/10.1001/jamaneurol.2015.0188.
[5] Sánchez S, Rincon F. Status epilepticus: epidemiology and public health needs. J Clin Med 2016;5:71. https://doi.org/10.3390/jcm5080071.
[6] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus - report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56:1515–23. https://doi.org/10.1111/epi.13121.
[7] Hocker S, Tatum WO, LaRoche S, Freeman WD. Refractory and super-refractory status epilepticus - an update. Curr Neurol Neurosci Rep 2014;14:452. https://doi.org/10.1007/s11910-014-0452-x.
[8] Aroor S, Shravan K, Mundkur SC, Jayakrishnan C, Rao SS. Super-refractory status epilepticus: a therapeutic challenge in paediatrics. J Clin Diagn Res 2017;8:SR01–4. https://doi.org/10.7860/JCDR/2017/25811.10485.
[9] Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134:2802–18. https://doi.org/10.1093/brain/awr215.
[10] Al-Otaibi FA, Hamani C, Lozano AM. Neuromodulation in epilepsy. Neurosurgery 2011;69:957–79. https://doi.org/10.1227/NEU.0b013e31822b30cd.
[11] Higgins JPT, Green S. Manual Cochrane de revisiones sistemáticas de intervenciones. Cochrane; 2011. p. 1–639. www.cochrane-handbook.org. [Accessed 26 July 2018].
[12] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41. https://doi.org/10.1016/j.ijsu.2010.02.007.
[13] Phillips B, Ball C, Sackett D. Oxford centre for evidence-based medicine - levels of evidence (March 2009). CEBM; 2009. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. [Accessed 26 July 2018].
[14] Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. Evid Based Med 2018;23:60–3. https://doi.org/10.1136/bmjebm-2017-110853.

[15] Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, Vist GE, Schünemann HJ, GRADE Working Group. Incorporating considerations of resources use into grading recommendations. BMJ 2008;336:1170–3. https://doi.org/10.1136/bmj.39504.506319.80.

[16] Cline JS, Roos K. Treatment of status epilepticus with electroconvulsive therapy. J ECT 2007;23:30–2. https://doi.org/10.1097/01.yct.0000263260.36915.2a.

[17] Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. Neurocritical Care 2010;12:204–10. https://doi.org/10.1007/s12028-009-9288-7.

[18] Ahmed J, Metrick M, Gilbert A, Glasson A, Singh R, Ambrous W, Brown L, Aykroyd L, Bobel K. Electroconvulsive therapy for super refractory status epilepticus. J ECT 2017;34. https://doi.org/10.1097/YCT.0000000000000450. e5–9.

[19] Yamazoe T, Okanishi T, Yamamoto A, Yamada T, Nishimura M, Fujimoto A, Enoki H, Yokota T, Sato K, Yamamoto T. New-onset refractory status epilepticus treated with vagus nerve stimulation: a case report. Seizure 2017;47:1–4. https://doi.org/10.1016/j.seizure.2017.02.011.

[20] De Hert V, Waterschooy L, Vonck K, Dermaut B, Verhelst H, Van Coster R, De Jaeger A, Van Roost D, Boon P. Vagus nerve stimulation for refractory status epilepticus. Eur J Neurol 2009;13(3):286–9. https://doi.org/10.1016/j.nurt.2008.12.003.

[21] Sierra-Marcos A, Maestro I, Rodríguez-Osorio X, Miró J, Donaire A, Aparicio J, Rumiá J, Forcadas M, Garamendi I, Pardo J, López J, Prieto Á, Plans G, Falip M, Carreño M. Successful outcome of episodes of status epilepticus after vagus nerve stimulation: a multicenter study. Eur J Neurol 2012;19:1219–23. https://doi.org/10.1111/j.1468-1331.2012.03707.x.

[22] Yazdi JS, Schumaker JA. Treatment of refractory status epilepticus with vagus nerve stimulator in an elderly patient. World Neurosurg 2016;95:620.e1–7. https://doi.org/10.1016/j.wneu.2016.08.017.

[23] Liu A, Pang T, Herman S, Pascual-Leone A, Rotenberg A. Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit. Seizure 2013;22:893–6. https://doi.org/10.1016/j.seizure.2013.06.014.

[24] VanHaerents S, Herman ST, Pang T, Pascual-Leone A, Shafi MM. Repetitive transcranial magnetic stimulation; A cost-effective and beneficial treatment option for refractory focal seizures. Clin Neurophysiol 2015;126:1840–2. https://doi.org/10.1016/j.clinph.2014.12.004.

[25] Thordstein M, Constantinescu R. Possibly lifesaving, noninvasive, EEG-guided neuromodulation in anesthesia-refractory partial status epilepticus. Epilepsy Behav 2012;25:468–72. https://doi.org/10.1016/j.yebeh.2012.07.026.

[26] Naro A, Pisani LR, Leo A, Molonia F, Bramanti P, Calabrò RS. Treatment of refractory generalized status epilepticus in a patient with unresponsive wakefulness syndrome: is neuromodulation the future? Epilepsy Behav 2015;50:96–7. https://doi.org/10.1016/j.yebeh.2015.06.038.

[27] Franzini A, Messina G, Marras C, Villani F, Cordella R, Broggi G. Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. Stereotact Funct Neurosurg 2008;86:373–81. https://doi.org/10.1159/000175800.

[28] Valentín A, Nguyen HQ, Skupenova AM, Agirre-Arrizubieta Z, Jewell S, Mullatti N, Moran NF, Richardson MP, Selway RP, Alarcón G. Centromedian thalamic nuclei deep brain stimulation in refractory status epilepticus. Brain Stimul 2012;5:594–8. https://doi.org/10.1016/j.brs.2011.10.002.

[29] Lee CY, Lim SN, Wu T, Lee ST. Successful treatment of refractory status epilepticus using anterior thalamic nuclei deep brain stimulation. World Neurosurg 2017;99:14–8. https://doi.org/10.1016/j.wneu.2016.11.097.

[30] Lehtimäki K, Långsjö JW, Ollikainen J, Heinonen H, Möttönen T, Tähtinen T, Haapasalo J, Tenhunen J, Katisko J, Öhman J. Peltola J Successful management of super-refractory status epilepticus with thalamic deep brain stimulation. Ann Neurol 2017;81:142–6. https://doi.org/10.1002/ana.24821.

[31] Carrasco González MD, Palomar M, Rovira R. Electroconvulsive therapy for status epilepticus. Ann Intern Med 1997;127:247–8. https://doi.org/10.7326/0003-4819-127-3-199708010-00026.

[32] Griesemer D, Kellner CH, Beale MD, Smith GM. Electroconvulsive therapy for treatment of intractable seizures. Initial findings in two children. Neurology 1997;49:1389–92. https://doi.org/10.1212/WNL.49.5.1389.

[33] Lisanby SH, Bazil CW, Resor SR, Nobler MS, Finck DA, Sackeim H. ECT in the treatment of status epilepticus. J ECT 2001;17:210–5. https://doi.org/10.1097/00124509-200109000-00013.

[34] Shin HW, O'Donovan CA, Boggs JG, Grefe A, Harper A, Bell WL, McCall WV, Rosenquist P. Successful ECT treatment for medically refractory non-convulsive status epilepticus in pediatric patient. Seizure 2011;20:433–6. https://doi.org/10.1016/j.seizure.2011.01.009.

[35] Mirás Veiga A, Moreno DC, Menéndez AI, Siscart IM, Fernández MD, Sánchez EG, González MGSF. Effectiveness of electroconvulsive therapy for refractory status epilepticus in febrile infection – related epilepsy syndrome. Neuropediatrics 2017;48:45–8. https://doi.org/10.1055/s-0036-1584939.

[36] Pinchotti DM, Abbott C, Quinn DK. Targeted electroconvulsive therapy for super refractory status epilepticus: a case report and literature review. Psychosomatics 2018;59:302–5. https://doi.org/10.1016/j.psym.2017.10.004.

[37] Chan EL, Lee WC, Koo CK, King HS, Woo CT, Ng SH. Electroconvulsive therapy for new-onset super-refractory status epilepticus. *Hong Kong Med J = Xianggang Yi Xue Za Zhi* 2018;24:307–10. https://doi.org/10.12809/hkmj154501.

[38] Winston KR, Levisohn P, Miller BR, Freeman J, Winston K. Vagal nerve stimulation for status epilepticus. Pediatr Neurosurg 2001;34:190–2. https://doi.org/10.1159/000056018.

[39] Patwardhan RV, Dellabadia J, Rashidi M, Grier L, Nanda A. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. Surg Neurol 2005;64:170–3. https://doi.org/10.1016/j.surneu.2004.11.026.

[40] Carreño M, Garcia-Alvarez D, Maestro I, Fernández S, Donaire A, Boget T, et al. Malignant autosomal dominant frontal lobe epilepsy with repeated episodes of status epilepticus: successful treatment with vagal nerve stimulation. Epileptic Disord 2010;12:155–8. https://doi.org/10.1684/epd.2010.0307.

[41] O'Neill BR, Valeriano J, Synowiec A, Thielmann D, Lane C, Wilberger J. Refractory status epilepticus treated with vagal nerve stimulation. Neurosurgery 2011;69:E1172–5. https://doi.org/10.1227/NEU.0b013e318223b979.

[42] Arhan E, Serdaroğlu A, Hirfanoğlu T, Kurt G. Aggravation of seizures and status epilepticus after vagal nerve stimulation therapy: the first pediatric case and review of the literature. Child's Nerv Syst 2018;34(9):3–5. https://doi.org/10.1007/s00381-018-3806-x.

[43] Al-Mufti F, Claassen J. Neurocritical care: status epilepticus review. Crit Care Clin 2014;30:751–64. https://doi.org/10.1016/j.ccc.2014.06.006.

[44] Schulze-Bonhage A. Long-term outcome in neurostimulation of epilepsy. Epilepsy Behav 2018:9–13. https://doi.org/10.1016/j.yebeh.2018.06.011.

[45] Bergey GK. Neurostimulation in the treatment of epilepsy. Exp Neurol 2013;244:87–95. https://doi.org/10.1016/j.expneurol.2013.04.004.

[46] Lambrecq V, Villéga F, Marchal C, Michel V, Guehl D, Rotge JY, Burbaud P. Refractory status epilepticus: electroconvulsive therapy as a possible therapeutic strategy. Seizure 2012;21:661–4. https://doi.org/10.1016/j.seizure.2012.07.010.

[47] Kalinowsky LB, Kennedy F. Observations in electric shock therapy applied to problems of epilepsy. J Nerv Ment Dis 1943;98(1):56–67. https://doi.org/10.1097/00005053-194307000-00006.

[48] Caplan G. Epilepsy treated by electrically induced convulsions. Br Med J 1945;1:511–2. https://doi.org/10.1136/bmj.1.4397.511.

[49] Viparelli U, Viparelli G. ECT and grand mal epilepsy. J ECT 1992;8(4):233–6. https://doi.org/10.1097/00041464-199212000-0000.

[50] Khalilov I, Holmes GL, Ben-Ari Y. In vitro formation of a secondary epileptogenic mirror focus by interhippocampal propagation of seizures. Nat Neurosci 2003;6:1079. https://doi.org/10.1038/nn1125.

[51] Sackeim H, Malitz S. Seizure threshold in electroconvulsive therapy. Arch Gen Psychiatr 1987;44:355–60. https://doi.org/10.1016/0006-3223(95)00262-F.

[52] Yang X, Wang X. Potential mechanisms and clinical applications of mild hypothermia and electroconvulsive therapy on refractory status epilepticus. Expert Rev Neurother 2015;15(2):135–44. https://doi.org/10.1586/14737175.2015.992415.

[53] Anschel DA. Letter to the Editor: use of pharmacologic coma for adults status epilepticus. Epilepsy and Behaivor 2005;6:292. https://doi.org/10.1016/j.yebeh.2004.11.021.

[54] Sackeim HA. Convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation. Clin Neurosci Res 2004;4:39–57. https://doi.org/10.1016/j.cnr.2004.06.013.

[55] Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. J ECT 1999;15:5–26. https://doi.org/10.1097/00124509-199903000-00003.

[56] Zeiler FA, Matuszczak M, Teitelbaum J, Gillman LM, Kazina CJ. Electroconvulsive therapy for refractory status epilepticus: a systematic review. Seizure 2016;35:23–32. https://doi.org/10.1016/j.seizure.2015.12.015.

[57] Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation in the treatment of refractory epilepsy. Neurotherapeutics 2009;6:228–37. https://doi.org/10.1016/j.nurt.2009.01.010.

[58] Cantarín-Extremera V, Ruíz-Falcó-Rojas ML, Tamaríz-Martel-Moreno A, García-Fernández M, Duat-Rodriguez A, Rivero-Martín B. Late-onset periodic bradycardia during vagus nerve stimulation in a pediatric patient. A new case and review of the literature. Eur J Paediatr Neurol 2016;20:678–83. https://doi.org/10.1016/j.ejpn.2016.02.014.

[59] Landau AM, Dyve S, Jakobsen S, Alstrup AKO, Gjedde A, Doudet DJ. Acute vagal nerve stimulation lowers α2 adrenoceptor availability: possible mechanism of therapeutic action. Brain Stimul 2015;8:702–7. https://doi.org/10.1016/j.brs.2015.02.003.

[60] Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Behav Rev 2005;29(3):493—550. https://doi.org/10.1016/j.neubiorev.2005.01.004.

[61] Marrosu F, Serra A, Maleci A, Puligheddu M, Biggio G, Piga M. Correlation between GABA(A) receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. Epilepsy Res 2003;55(1–2):59—70. https://doi.org/10.1016/s0920-1211(03)00107-4.

[62] Al Omari AI, Alzoubi FQ, Alsalem MM, Aburahma SK, Mardini DT, Castellanos PF. The vagal nerve stimulation outcome, and laryngeal effect: otolaryngologists roles and perspective. Am J Otolaryngol - Head Neck Med Surg 2017;38:408–13. https://doi.org/10.1016/j.amjoto.2017.03.011.

[63] Lanska DJJL. Corning and vagal nerve stimulation for seizures in the 1880s. Neurology 2002;58:452–9. https://doi.org/10.1212/WNL.58.3.452.

[64] Chase MH, Nakamura Y, Clemente CD, Sterman MB. Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. Brain Res 1967;5:236–49. https://doi.org/10.1016/0006-8993(67)90089-3.

[65] Zanchetti A, Wang SC, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol 1952;4:357–61. https://doi.org/10.1016/0013-4694(52)90064-3.

[66] Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. VNS for refractory status epilepticus. Epilepsy Res 2015;112:100–13. https://doi.org/10.1016/j.eplepsyres.2015.02.014.
[67] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56. https://doi.org/10.1016/S1474-4422(03)00321-1.
[68] Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16. https://doi.org/10.1016/S0168-5597(97)00096-8.
[69] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S. Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39. https://doi.org/10.1016/j.clinph.2009.08.016.
[70] Anand S, Hotson J. Transcranial magnetic stimulation: neurophysiological applications and safety. Brain Cogn 2002;50:366–86. https://doi.org/10.1016/S0278-2626(02)00512-2.
[71] Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol Evoked Potentials 1993;89:120–30. https://doi.org/10.1016/0168-5597(93)90094-6.
[72] Pascual-Leone Á, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–58. https://doi.org/10.1093/brain/117.4.847.
[73] Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci 2005;28:377–401. https://doi.org/10.1146/annurev.neuro.27.070203.144216.
[74] Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ, Pascual-Leone A, Rotenberg A. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 2007;10:521–8. https://doi.org/10.1016/j.yebeh.2007.03.004.
[75] Moradi Chameh H, Janahmadi M, Semnanian S, Shojaei A, Mirnajafi-Zadeh J. Effect of low frequency repetitive transcranial magnetic stimulation on kindling-induced changes in electrophysiological properties of rat CA1 pyramidal neurons. Brain Res 2015;1606:34–43. https://doi.org/10.1016/j.nrainres.2015.02.023.
[76] Yadollahpour A, Firouzabadi SM, Shahpari M, Mirnajafi-Zadeh J. Repetitive transcranial magnetic stimulation decreases the kindling induced synaptic potentiation: effects of frequency and coil shape. Epilepsy Res 2014;108(2):190–201. https://doi.org/10.1016/j.eplepyres.2013.11.023.
[77] Van Haerents S, Herman ST, Pang T, Pascual-Leone A, Shafi MM. Repetitive transcranial magnetic stimulation; a cost-effective and beneficial treatment option for refractory focal seizures. Clin Neurophysiol 2015;126(9):1840–2. https://doi.org/10.1016/j.clinph.2014.12.004.
[78] Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Chris Baeken, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125(11):2150–206. https://doi.org/10.1016/j.clinph.2014.05.021.
[79] Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua. Epilepsy Behav 2009;14:253–7. https://doi.org/10.1016/j.yebeh.2008.09.007.
[80] Morales OG, Henry ME, Nobler MS, Wassermann EM, Lisanby SH. Electroconvulsive therapy and repetitive transcranial magnetic stimulation in children and adolescents: a review and report of two cases of epilepsia partialis continua. *Child Adolesc Psychiatr* Clin N Am 2005;14:193–210. https://doi.org/10.1016/j.chc.2004.07.010.
[82] William J. Marks J. *Deep brain stimulation management*. San Francisco California: Cambridge University Press; 2010. https://doi.org/10.1017/CBO9780511763281.
[83] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x.
[84] Jahanshahi A, Mirnajafi-Zadeh J, Javan M, Mohammad-Zadeh M, rohani r. The antiepileptogenic effect of electrical stimulation at different low frequencies is accompanied with change in adenosine receptors gene expression in rats. Epilepsia 2009;50(7):1768–79. https://doi.org/10.1111/j.1528-1167.2009.02088.x.
[85] Schumucker C, Bluemle A, Briel M, Portalupi S, Lang B, Motschall E, et al. A protocol for a systematic review on the impact of unpublished studies and studies published in the gray literature in meta-analyses. Syst Rev 2013;2(1):24. https://doi.org/10.1186/2046-4053-2-24.