INPLASY PROTOCOL

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Conflicts of interest:
None declared.

The efficacy and safety of neuromodulation in refractory epilepsy: a systematic review and network meta-analysis

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Review question / Objective: **To assess the efficacy and safety of different neuromodulation applied to the refractory epilepsy and provide a better choice for clinical practice.**
Condition being studied: **Epilepsy is a frequent neurologic illness defined by bursts of hypersynchronized neural network activity that afflict about 1% of the global population. Unfortunately, roughly 30% of people with drug-resistant epilepsy (DRE) continue to experience seizures despite three anti-seizure drugs. In most cases, resective surgery, as the first-line treatment for DRE, is considered a curative therapy for achieving long-term seizure-free status, but about half of patients are not candidates for surgery due to a variety of factors such as multiple/diffuse/widespread seizure foci, epileptic foci arising from eloquent, primary generalized epilepsy, or patients unwilling to undergo surgery. Neuromodulation, albeit palliative, is an important alternative treatment for these individuals to prevent or decrease ictal episodes, which can affect the nervous system in a variety of ways.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 April 2022 and was last updated on 07 April 2022 (registration number INPLASY202240042).

INTRODUCTION

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Condition being studied: **Epilepsy is a frequent neurologic illness defined by bursts of hypersynchronized neural network activity that afflict about 1% of the global population. Unfortunately, roughly 30% of people with drug-resistant epilepsy (DRE) continue to experience seizures**

despite three anti-seizure drugs. In most cases, resective surgery, as the first-line treatment for DRE, is considered a curative therapy for achieving long-term seizure-free status, but about half of patients are not candidates for surgery due to a variety of factors such as multiple/diffuse/widespread seizure foci, epileptic foci arising from eloquent, primary generalized epilepsy, or patients unwilling to undergo surgery. Neuromodulation, albeit palliative, is an important alternative treatment for these individuals to prevent or decrease ictal episodes, which can affect the nervous system in a variety of ways. Various techniques of neuromodulation including invasive therapies: 1) vagus nerve stimulation (VNS), 2) deep brain stimulation (DBS), 3) responsive neurostimulation (RNS) and non-invasive ones: 4) transcutaneous VNS (tVNS), 5) repetitive transcranial magnetic stimulation (rTMS), 6) transcranial direct current stimulation (tDCS), 7) trigeminal nerve stimulation (TNS), have been studied in controlling DRE over the past decades.Only RNS (based on detection of ictal EEG patterns) and a portion of VNS (based on detection of tachycardia) were closed-loop in clinical practice among these neuromodulation therapies. In 1997, 2014, and 2018, the Food and Drug Administration (FDA) approved VNS, RNS, and the anterior nucleus of the thalamus-DBS (ANT-DBS) for the treatment of DRE in the United States. Furthermore, in Europe, tVNS was approved with the three neuromodulation therapies described above. This study will cover the history, mechanism, indications, applications, efficacy, and safety of several neuromodulation techniques for DRE.

METHODS

Participant or population: Patients diagnosed with refractory epilepsy whether they suffered from focal, and/or generalized, and/or other types of seizures.

Intervention: brain stimulation therapies including anterior thalamic stimulation (ANT-DBS), centromedian thalamic stimulation (CMT-DBS), cerebellar stimulation (CB-DBS), hippocampal stimulation (HC-DBS), nucleus accumbens stimulation (NAC-DBS), responsive cortical stimulation (RNS), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), trigeminal nerve stimulation (TNS), transcutaneous vagus nerve stimulation (taVNS), vagus nerve stimulation (VNS).

Comparator: Sham stimulation or stimulation-OFF.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: We set the inclusion criteria as follows: 1) study type: RCT; 2) language restriction: only available in English; 3) participants: patients diagnosed with refractory epilepsy whether they suffered from focal, and/or generalized, and/or other types of seizures; 4) intervention: brain stimulation therapies including anterior thalamic stimulation (ANT-DBS), centromedian thalamic stimulation (CMT-DBS), cerebellar stimulation (CB-DBS), hippocampal stimulation (HC-DBS), nucleus accumbens stimulation (NAC-DBS), responsive cortical stimulation (RNS), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), trigeminal nerve stimulation (TNS), transcutaneous vagus nerve stimulation (taVNS), vagus nerve stimulation (VNS) and corresponding control; 5) outcomes: efficacy outcomes including absolute change in seizures per month, percent changes in monthly seizure frequency and 50% responder rate which defined as the number of patients achieving ≥50% reduction in seizure frequency. Safety outcomes including adverse events (AEs). Included RCTs were not requested to supply all the outcomes mentioned above.We set the exclusion criteria as follows: 1) study type: retrospective studies, cohort studies, case reviews and case reports.

Information sources: Medline, Embase, Cochrane library and the Clinicaltrials.gov.

Main outcome(s): Efficacy outcomes including absolute change in seizures per

month, percent changes in monthly seizure frequency and 50% responder rate which defined as the number of patients achieving ≥50% reduction in seizure frequency. Safety outcomes including adverse events (AEs).

Quality assessment / Risk of bias analysis: The risk of bias plot was evaluated with the Review Manager 5.3 software. The uniform criteria of the Cochrane collaboration were used to assess the risk of bias for RCTs, which included: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. Each bias criterion was classified as "low", "high", or "unclear".

Strategy of data synthesis: The outcome data that mentioned above were retrieved preferable from study-reported modified results or original intention-to-treat results. We estimated the absolute or percentage seizure frequency change from the reported data when authors of included RCTs did not mention it. We used Review Manager 5.3 software to perform pairwise meta-analysis of direct evidence. The relative risk (RR) and standardised mean difference (SMD) with 95% confidence interval (95% CI) were analyzed and calculated with a random effect model for the dichotomous and continuous outcomes, respectively. We then estimated heterogeneity through the I2 statistic as follows: I2 < 30% suggests "low heterogeneity"; I2 between 30% and 50% indicates "moderate heterogeneity"; I2 > 50% denotes "substantial heterogeneity". A sensitivity analysis was also carried out to explore the stability of the consolidated results. Secondly, network meta-analysis was performed for each outcome using R 3.5.2 software. Treatment efficacy and safety was compared via direct and indirect evidence using the RR values, along with 95% CrI. To rank the performance of 11 brain stimulation therapies and control in each outcome, the surface under curve ranking area (SUCRA) was created. For each outcome, a larger SUCRA value indicated a better rank for the intervention. The ranking probabilities were calculated as cumulative probabilities with each intervention being ranked. For all the analyses, two tailed tests were performed and a P value < 0.05 was considered to be statistically significant.

Subgroup analysis: Subgourp analysis will be performed on the influence of different kinds of refractory epilepsy such as focal seizure and generalized seizure.

Sensitivity analysis: For the part of high heterogeneity in pair-wise comparison, a sensitivity analysis was conducted for further analysis.

Language: English.

Country(ies) involved: China.

Keywords: Neuromodulation; refractory epilepsy; systematic review; network meta-analysis.

Contributions of each author:
Author 1 - Xin Wu.
Author 2 - Tao Xue.