Efficacy of Non-Invasive Neuromodulation in the Treatment of Drug-Resistant Epilepsy

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Abstract

Objective: Affecting over 50 million individuals worldwide, epilepsy is one of the most common neurological diseases and has significant impacts on quality of life. In patients with epilepsy, approximately 30% experience drug-resistant, or refractory epilepsy. Neuromodulation methods can often be suggested by clinicians if surgical resection criteria are unmet. Transcranial magnetic stimulation (TMS), a brain stimulation method, has been approved by the FDA and is widely used in patients with depression and mood disorders. However, the efficacy of TMS and similar non-invasive neuromodulation approaches in drug-resistant epilepsy has been unclear**.** **Aim:** In this review, the goal is to evaluate the safety and efficacy of different noninvasive neuromodulation techniques in reducing seizure frequency and improving quality of life by analyzing results from recent clinical trials in epilepsy patients. **Methods**: Randomized clinical trials published between 2015-present from PubMed, Scopus and Embase that utilize non-invasive neuromodulation methods in patients with drug-resistant epilepsy are reviewed and critically appraised for primary findings. **Results**: Overall, it is generally accepted that non-invasive neuromodulation methods are safe with minimal adverse effects. However, findings regarding the effectiveness in reducing seizure or improving life quality of non-invasive methods are mainly inconclusive. The lack of direct comparison between two or more neuromodulation methods at clinical trials proposes a need for the future examination or combined trials.

Key Words: “seizures”, “epilepsy”, “TMS”, “rTMS”, “tACS”, “brain stimulation”, “non-invasive neuromodulation”, “tDCS”, “ta-VNS”, “transcranial stimulation”, “clinical trials”

Abbreviations: Quality of Life (QoL), Adverse Event (AE), Seizure Frequency (SF), antiepileptic drugs (ADE)**,** drug-refractory epilepsy (DRE), Transcranial magnetic stimulation (TMS), Repetitive Transcranial magnetic stimulation (rTMS), Transcranial direct current stimulation (tDCS), Transcranial alternating current stimulation (tACS), Non-invasive brain stimulation (NIBS), Transcutaneous VNS (tVNS), Transcutaneous auricular VNS (ta-VNS).

Purpose of Review: *Is there efficacy associated with non-invasive neuromodulation methods (I) in terms of safety, quality of life improvement, and reduction of seizure frequency (O) in patients with drug-resistant epilepsy (P)?*

Introduction

Epilepsy is one of the most common neurological diseases, with around 50 million individuals being affected worldwide (WHO, 2023). Despite being the first line therapy, around 30% of patients with epilepsy are drug-resistant to antiepileptic drugs (ADEs) (Kalilani et al., 2018). This suggests a need for other treatment methods, including surgical resection for the removal of visible lesions and neurostimulation. Since many patients do not match the criteria and are at high risk for surgery, noninvasive stimulation methods such as repetitive Transcranial Magnetic Stimulation (rTMS), which utilizes the electromagnetic coil device to deliver magnetic pulses that stimulate specific brain region(s), can be an option. Some of the other non-invasive methods, including Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), are currently being carried out at clinical trials or pilot epilepsy studies.

Despite the wide number of controlled clinical trials involving TMS being carried out to study depression, moods and episodic memory; published trials of TMS as a treatment for epilepsy are sparse (Davis et al., 2020). TMS was proven to be a safe measure with a low adverse rate of 17.1% (Bae et al., 2007) which involves the repeated stimulation of electromagnetic current at low frequency to reduce cortical excitability. Repetitive TMS (rTMS) refers to the repeated delivery of TMS pulses to a specific brain region. However it did not receive much focus in epilepsy at clinical trials compared to invasive methods involving implantation devices such as Deep Brain Stimulation. In this review, the goal is to investigate and compare the results of randomized controlled trials in human subjects with rTMS as well as other novel techniques to draw a comprehensive understanding of the current state of non-invasive brain stimulation (NIBS) as a treatment paradigm for drug-refractory epilepsy (DRE). Overall, findings from pilot or randomized clinical trials conducted in recent years are critically appraised and compared to advance our understanding of the therapeutic potential of NIBS in patients with DRE.

Basic Mechanism of Non-Invasive Brain Stimulation (NIBS)

Developed based on the principles of electromagnetic induction by Michael Faraday in 1831, TMS is a non-invasive technique which utilizes magnetic fields to induce electrical stimulation to the brain cortex free of pain or direct contact (A.T. Barker et al., 1985). Repetitive TMS (rTMS) delivers repetitive pulses of low frequency that alter neural networks and guide neuronal plasticity in the long term (Ziemann et al., 2001). At certain intensity, deep peripheral nerves and facial nerves can also be targets of stimulation, without any contact or implantation (A.T. Barker, 1991). Depending on the frequency, rTMS protocols can be defined to increase (high-frequency, >5Hz) or decrease (typically <1Hz) cortical excitability. In the treatment of epilepsy specifically, most clinical trials utilize low-frequency rTMS to minimize the risk of inducing or worsening seizures as a result of stimulation.

In tDCS, continuous electrical stimulation is delivered through electrode(s) (cathode, anode) placed directly on a patient's scalp. A subtype known as high-definition tDCS (HD-tDCS) has a smaller, more focused target. Another similar method that utilizes electrical stimulation is tACS which applies in an alternating, or oscillating manner between electrodes. A meta-analysis has shown that both TMS and tDCS have positive effects in working memory in patients with neurological disorders (stroke, dementia, depression, traumatic brain injury,...) but not in other cognitive domains (Begemann et al., 2020). It is notable that no epilepsy patients were included in that review. Other systematic reviews have also indicated that tDCS is effective in improving ADL capacity after stroke (Elsner et al., 2017) and bipolar depression (Sudbrack-Oliveira et al., 2021).

Finally, transcutaneous VNS (tVNS) is another neuromodulation technique that utilizes electrical stimulation to the vagus nerve. In contrast to the widely known and FDA approved VNS, the term 'transcutaneous' implies that electrical stimulation is delivered through skin, eliminating the risks associated with invasive implantation. In an early 'proof of concept' clinical trial published by Stefan et al. in 2012, tVNS was considered feasible, generally safe and tolerable stimulation in patients with refractory epilepsy. In this review, we primarily include studies that stimulate the auricular branch (ta-VNS). Overall, tACS, tDCS, ta-VNS and rTMS are the primary reviewed NIBS methods.

Methods

Literature Search

To examine this topic, 7 defined search criteria were applied for an initial search: **1) Non-invasive modulation** (""rTMS" OR "tDCS" OR "tACS" OR "ta-VNS" OR "brain stimulation" OR "non-invasive neuromodulation" OR "non-invasive brain stimulation" and the full terminology); **2) Epilepsy** ("Epilepsy" OR "seizures"); **3) Drug-resistance** ("Drug Resistant Epilepsy" OR "refractory" OR "drug resistant"); **4) Clinical Trial** (Either "controlled clinical trial" or Clinical trial Filter); **5) Human** (Either "Human" or Human Filter); **6) English Language** (Filter); **7) Date** (2015-2024 only). The chosen databases are *PubMed*, *Scopus* and *EMBASE*. While *PubMed* and *EMBASE* are widely used in biomedical or neuroscience research, Scopus provides a multidisciplinary perspective.

This initial search yielded a total of **137** articles in Pubmed, **202** in Embase and **191** in Scopus (refer to *Supplemental Material*). Abstracts and case studies were not included for further analysis. Some systematic reviews and selected narrative reviews are included to provide existing stance and data for the construction of introduction/background. One systematic review conducted by Wang et al. (2022) in patients with neuropathy is included to establish a background of the safety of non-invasive treatment.

Selection Criteria

Utilizing the PI(C)O formula, the aim is to study the effects of non-invasive methods in the target population of patients with drug-resistant epilepsy (*Population*). Several subtypes of non-invasive neuromodulation such as repetitive transcranial magnetic stimulation (rTMS), transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), and transcutaneous auricular Vagus Nerve Stimulation (ta-VNS) are subjected to review (*Intervention*). Primary findings are from clinical trials, most of which are randomized, double-blinded, and sham-controlled. In most of the included clinical trials, findings are compared with baseline and across treatment vs control (sham) groups but none are directly across different NIBS. Selected articles were then subjected under critical appraisal using some qualitative measures from the Joanna Briggs Institute Critical Appraisal Tool for randomized controlled trials (T.H.Barker et al., 2023). The studies were not given a specific score but were excluded if numerous biases or unclear methods were present. Additional findings or reviews on the physics of transcranial stimulation in comparison to invasive implantation is included in this review to address the rationale for the topic.

Table One: Selection Criteria for Clinical Trials

Domain	Inclusion criteria	Exclusion criteria
Population	Studies in adults, or ≥ 15 to 65 years old ; patients with DRE	Exclusively pediatric population, patients without DRE, or non-human subjects
Intervention	Directly tests one (or more) of NIBS treatment protocols on tACS/ tDCS/ ta-VNS/ rTMS	Does not involve modality of interest (ie. invasive methods, deep brain stimulation, etc)
(Comparison)	N/A	N/A
Outcome	Studies that evaluate at least two out of three primary outcomes (SF/AE/QoL)	Studies that evaluate other outcomes (oscillation analysis, memory, etc) or other diseases
Study Design	Randomized, blinded, controlled trials	Open-label trials, non-randomized studies
Language	English	Not in English

Subsequently, the majority of evidence being used comes directly from clinical trials in patients with drug-refractory epilepsy. Certain studies had specified subtype of DRE such as focal or multifocal DRE. The primary measures (*Outcomes*) investigated are quality of life, safety and seizure frequency (SF), which are all widely used measures of efficacy in the study of neurological diseases as well as epilepsy. To answer the research question, evidence will be drawn separately on each aspect of the outcomes (O).

Clinical trials that focus on neuromodulation as a treatment for other neurological diseases, neuropathy or psychiatric disorders are excluded. Some findings on safety and efficacy of these methods in other neurological diseases such as stroke, depression or mood disorders from systematic reviews are referenced to establish the foundation on the primary use of NIBS. After a screening of titles and abstracts for the above selection criteria, 6 clinical trials were included for primary analysis.

Table 2: Results — Summary of Clinical Trials (6)

First Author, Year Published	Study Design	Sample Population	NIBS technique	Treatment Design	Outcomes Assessed		
					Adverse Events (AE)	Seizure Frequency	Quality of Life
San-Juan et al., 2022	Pilot randomized, double-blind, placebo-controlled clinical trial	Multifocal DRE age 15-65	tACS	n total = 23; 3 arms (placebo, 2mA/3Hz for 30 min treatment, 60-min treatment)	Tingling sensation, 1 seizure occurred immediately after session in placebo group and 2 seizures in tACS-60	No overall significant reduction	N/A
D. Yang et al., 2020	Randomized, double-blind, sham-controlled clinical trial	Focal DRE age 18-60	tDCS	n total = 70 ; 3 arms (sham, 20-min treatment, 20-min x 2 treatment)	Minor (tingling/itching sensation), 2 seizures in sham group, 3 seizures in Group 3	Some significant reduction in both treatment protocols, Group 3 more effective by the end of 2 weeks.	No improvement
Rezakhani et al., 2022	Randomized, double blind, placebo-controlled clinical trial	Focal DRE age >= 18	HD-tDCS	n total = 20 ; 2 arms (sham, 30-min treatment)	None reported, no induced seizures throughout treatment sessions	Significant reduction across all recorded time points	Overall higher QoLIE-89 score after treatment.
H. Yang et al., 2023	Randomized, double-blind, controlled clinical trial	Any DRE age 18-65	ta-VNS	n total= 112 (1Hz control, 25 Hz treatment)	Minor AEs (13.16% occurrence rate in active vs 22.22% in control); no serious AEs in either group	Significant reduction by 30.75% in treatment group at week-20	No improvement
Bauer et al., 2016	Randomized, double-blind, controlled clinical trial	Focal/Generalized DRE age 18-65	t-VNS (ta-VNS)	n total = 76 ; 2 arms (active 1Hz control, 25Hz treatment)	Overall mild/moderate AEs were reported. >80% in both groups reported treatment emergent AEs (fatigue, headache, nausea, dizziness, ...). Severe AEs were reported in 7.7% of AEs (control) compared to 16.2% (treatment)	Significant reduction in treatment group at the week-20 time point	No improvement
Seynaeve et al., 2016	Randomized, double-blind crossover, sham-controlled clinical trial	Focal neocortical DRE age 16-75	rTMS	n total = 11; patients undergo 2 weeks of randomized treatment order with either sham, figure-9 or round coil.	2 cases with serious AE (possible induced seizures), other minor AEs (headaches, fatigue, ...)	No overall significant reduction	Some improvement in half of patients

(n represents the final number of participants/ after exclusion)

Results

Safety of Non-invasive Neuromodulation methods

Previous literature indicates that non-invasive neuromodulation methods are generally safe for human subjects. In a systematic review conducted by Wang et al. published in 2022, adverse events in the reviewed clinical studies were mild and subsided following termination of the treatment in patients with chemotherapy-induced peripheral neuropathy. Here, we review safety outcomes from clinical trials that target patients with refractory epilepsy.

It has been established that tACS is a promising non-invasive stimulation method for the treatment of neuropsychiatric diseases. However, its efficacy in the field of epilepsy is largely unknown. The study by San-Juan et al. is a pilot randomized controlled clinical trial with 3 parallel groups which aims to evaluate the safety and effectiveness of tACS as a neuromodulation treatment of pharmaco-resistant epilepsy. From this clinical trial, only minor adverse events in some patients were recorded. In detail, 21% of patients experience a "tingling sensation" which promptly subsided after the treatment. (San-Juan et al., 2022). The rare and transient nature of these adverse events suggest that tACS is a generally safe therapeutic option.

Two of the most recent clinical studies that assess the safety and effects of transcranial direct current stimulation (tDCS) in DRE are subjected for review. In a double-blinded, randomized clinical trial, Yang et al. (2020) evaluate the safety and change in seizure frequency in patients with refractory focal epilepsy following treatment with tDCS. The clinical trial has 3 arms (sham control group, treatment of 20-min, treatment 20-min x2) in patients with refractory focal epilepsy. In this multicenter study, safety evaluation indicates over 70% of patients in the treatment arms reported mild itching sensation at location of electrode placement during administration of tDCS. Five seizures occurred throughout the study, two of which came from sham/control arm and three came from the treatment arm. Analysis of seizure semiology indicates that the onset of these seizures may not be due to cortical excitability caused by tDCS, although further clinical studies and evidence is needed in this area (D. Yang et al., 2020). In another randomized clinical trial that investigates high-definition cathodal tDCS (HD-tDCS), patients in the treatment group were subjected to HD-tDCS stimulation (2mA) for 30 minutes/5 days a week for 2 weeks. Researchers reported no adverse effects or induced seizures in all patients (Rezakhani et al., 2022). This is somewhat unexpected, given that HD-tDCS is a subtype of tDCS with smaller surfaces and higher focal accuracy through direct contact.

In recent years, the novel transcutaneous auricular Vagus Nerve Stimulation (ta-VNS) device has also emerged as a promising alternative for the invasive VNS. The study conducted by Yang et al. (2023) is a randomized, double-blinded clinical trial which assesses the efficacy, safety and health-related quality of life for patients with drug-resistant epilepsy. In this study, a

total of 150 patients were enrolled and randomly assigned into either control group, or active stimulation group. It is important to note that several participants were excluded throughout the trial and only 112 were included in final analysis. The most common adverse events including sleep disturbance, pain, local skin discomfort and flu-like symptoms were considered minor and no severe adverse events were noted in either group (H. Yang et al., 2023). This suggests the safety of ta-VNS, consistent with previous pilot study by Stefan et al. (2012). It is also particularly useful as evidence when comparing ta-VNS against the well-known VNS, a traditionally invasive method that has proven to be effective in epilepsy treatment. However, the relatively high drop-out rate is a potential limitation of this study.

Another clinical trial conducted by Bauer et al. (2016) is a randomized, double-blinded clinical trial of 39 patients in the treatment group and 37 controls receiving ta-VNS stimulation frequency of 25 Hz and 1Hz, respectively. Adult patients with either generalized seizures or focal epilepsy on a stable AEDs regimen prior to and throughout the study period of 28 weeks. Serious adverse events were reported in 4 control patients and 3 treated patients, leading to their termination from the study. The only reported case of 'seizure worsening' was in the control group, suggesting non-causal by tVNS treatment. Other minor adverse events were commonly reported in both control (33/39 patients) and treatment group (32/37 patients).

Lastly, the safety and efficacy of repetitive TMS (rTMS) in a population of patients with refractory focal epilepsy was examined by Seynaeve et al. in a crossover clinical trial published in 2016. Low-frequency stimulation (0.5 Hz) was delivered in 10 sessions throughout a two-week period. Minor adverse events include fatigue, difficulty concentrating, and hearing problems. In two cases, an increase in SF was abruptly observed. In one of these patients, severe headache was also reported (Seynaeve et al., 2016). Despite the low number of adverse events, the presence of serious adverse events is notable and the heterogeneity of findings suggest a need for a mechanistic approach against current protocols. Other than the small sample size, another limitation to note is the crossover design, thus a lack of parallel placebo-control vs. treatment group in this study.

Effects on Seizure Frequency (SF)

Primary findings indicate no significant reduction of Seizure Frequency (SF) in tACS. In the study conducted by San-Juan et al., treatment with either tACS-30 or tACS-60 did not significantly reduce/alter seizure frequency. The study also highlights a need for further testing of tACS in patients with multifocal drug-resistant epilepsy using other parameters to make a full conclusion (San-Juan et al., 2022).

In contrast, the effectiveness of tDCS was highlighted in both reviewed clinical trials. Significant reduction was found especially in the 2x20min (group 3) daily protocol compared to

20-min (group 3) daily protocol. Specifically, in group 3, there was a 59.94–48.96% greater reduction of seizure frequency in comparison to the control group by the end of 14 days. Efficacy of group 2 protocol was shown only at earlier time points but not at day 14 (D. Yang et al., 2020). Similarly, patients receiving HD-tDCS treatment in Rezakhani et al. show significant reduction in SF, from a similar baseline compared to sham-controlled groups. In addition, a significant decrease in Interictal Epileptiform Discharge (IEDs) recorded from EEG was found. (Rezakhani et al., 2022). The possibility of variations in efficacy based on repetition or duration of tDCS use indicate a need for further testing and optimization of tDCS protocols in DRE patients.

In the study by Yang et al. (2023) on ta-VNS, overall there is a significantly higher responder rate (defined as SF >= 50%) found by week 20 in the active group compared to the control group. This is consistent with a prior randomized clinical trial that observed over 40% (n=98) SF reduction from baseline (Rong et al., 2014). In Bauer et al. (2016), significant reduction in SF was also found in participants that completed full treatment period. Strikingly, complete seizure freedom was only achieved in 3/39 (control group) and 1/37 (active treatment group), which is a serious drawback.

The study on rTMS by Seynaeve et al. (2016) indicates no significant changes in the average SF across participants. However, it is notable that an individual patient had up to 48% seizure reduction following treatment while a negative effect on SF was found in two other patients These contrary outcomes present a lack of evidence and support for usage of TMS in epilepsy.

Effects on Quality of Life (QoL)

It is important to note that while Seizure Frequency was identified as a primary measure in all of the included studies on refractory epilepsy in this review, follow-up assessments on Quality of Life (QoL) were only conducted at some of the clinical trials as secondary outcomes. In the study by Yang et al. on ta-VNS, several questionnaires including the Hamilton Anxiety Scale (HAMA), depression scale, and other cognitive assessments were carried out at follow-up interviews. Despite the rigorous amount of assessments on QoL, no significant improvement was observed in quality of life. In contrast to the significant reduction in SF of this study, the lack of improvement in QoL or cognitive outcomes indicate a lack of correlation between the two (H. Yang et al., 2023).

An analysis on QoL in the tDCS study indicates no significant difference between control vs. treatment groups. Evaluation of the Quality of Life in Epilepsy-31 (QOLIE-31) assessment was performed. Once again, despite the reduction in SF in this study, no significant improvement in QoL was observed. Potential limitations or bias factors, such as “use of antiepileptic drugs” were noted (D. Yang et al., 2020). In the trial on HD-tDCS, some significant increase in MoCA

score, which aims to assess working memory, was found only at the 2-week follow up. A more consistent and improvement in the overall QoLIE-89 outcome was found at the 3-month follow up. Some of the variables that have significant positive improvement include: pain, attention concentration, social support and health perception (Rezakhani et al., 2022).

In Bauer et al. (2016), QoL measures including QOLIE-31-P and other depression/symptom assessments show no significant changes by the end of the study, and no significant difference between two arms of ta-VNS. Similarly, the rTMS study conducted by Seynaeve et al. (2016) also utilized QOLIE-31 system. It was found that half of the patients in this study had some improvement in QoL score, suggesting some efficacy in cognition or mood regardless of a lack in SF reduction.

Discussion

In many patients with drug-resistant epilepsy, neuromodulation method(s) is usually offered by clinicians with the goal of reducing seizure burden. While non-invasive neurostimulation methods provide transcranial stimulation for patients, invasive methods usually require surgical procedure for placement of implant/stimulation devices. In an overview conducted by Parihar et al. (2020), the authors put forth a classification for the invasiveness/ non-invasiveness of different neurostimulation paradigms. In this review, we included clinical trials on three out of four of the common non-invasive techniques presented. The inclusion of the technique (tACS) further brings in a perspective for recent protocols under development.

One common strength of clinical studies in this review lies in the comprehensiveness and details regarding safety and adverse effects. Consistent with previous findings, the reviewed neuromodulation techniques have been found to be generally safe and well-tolerated with few adverse events. Few cases of possibly induced seizures were reported, although it is unclear whether stimulation was the true cause. Regarding seizure frequency, rTMS and tACS have no significant findings while both tDCS trials, and both ta-VNS trials show positive reduction. The lack of effectiveness in rTMS treatment is consistent with previous findings (Theodore et al., 2002).

It is important to note of NIBS's limitation to fully lift the burden or to grant disease freedom in patients. Most of the reviewed studies did not find any significant improvement in cognition or QoL following treatment sessions. Significant improvement was found in the rTMS study conducted by Seynaeve et al. (2016), with no improvement in SF. The clinical findings from Rezakhani et al. (2022) in tDCS was the only treatment group with improvement in both overall QoL measure (but not MoCA) and seizure frequency reduction. Overall, the lack of correlative findings between SF and QoL suggests a need for the identification of underlying biases or mechanisms of the designed protocols.

One of the main limitations of this review is the inclusion of different subtypes of drug-refractory epilepsy. Different seizure localization (generalized vs multifocal vs focal), hence different etiology, can contribute to the efficacy and outcome of each treatment method. It

was also concluded that while the field of neuromodulation continues to receive much attention and has promising potential, there has been no clinical trials that directly compare either two or multiple neurostimulation methods in human subjects (Parihar et al., 2020). Not only does this pose a challenge as we draw a comparison between non-invasive and invasive treatment methods, it also highlights the need for such protocols to be compared and tested in conjunction at combined clinical trials.

Conclusion

This paper reviewed clinical trials of different non-invasive neuromodulation methods in patients with drug-resistant epilepsy to examine safety, efficacy and any improvement in life quality. Among the recent trials, non-invasive neuromodulation methods are generally well-tolerated with minimal adverse events across clinical trials. The most notable and serious adverse event was the occurrence of additional seizures in a few cases. Due to similar etiology compared to baseline in patients with drug-refractory epilepsy, further investigation is needed to confirm if the recorded adverse events are due to stimulation/treatment. Findings on Seizure Frequency (SF) show significant reduction in 4/6 reviewed clinical trials. Specifically, tDCS and ta-VNS treatments had consistent reduction but not in rTMS and tACS. In the studies that assessed Quality of Life (QoL) or memory (MoCA scale), most participants did not experience an improvement. The sparsity in usage and testing of non-invasive neuromodulation methods in refractory epilepsy suggest a need for further clinical trials and comparative trials to be conducted. Evidence from this study solidifies the strong safety profile of NIBS across different techniques but is insufficient to prove NIBS efficacy.

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Supplemental Material:

Search Dates: 03/27/2024 and 04/01/2024

1) **Search Database: Pubmed**

Search ID	Search Terms	Results
#1 Modulation	"rTMS" OR "tDCS" OR "tACS" OR "ta-VNS" OR "brain stimulation" OR "non-invasive neuromodulation" OR "non-invasive brain stimulation" OR "Transcranial Magnetic Stimulation" OR "Transcranial direct current stimulation" OR "transcranial alternating current stimulation" OR "Transcranial Direct Current Stimulation"[Mesh] OR "Transcranial Magnetic Stimulation"[Mesh] OR "Vagus Nerve Stimulation"[Mesh]	**55,006**
#2 Epilepsy	"Epilepsy" OR "seizures" OR "Epilepsy"[Mesh]	**257,375**
#3 Refractory	"Drug Resistant Epilepsy"[Mesh] OR "refractory" OR "drug resistant"	**221,992**
#4 Combine	#1 AND #2 AND #3	**1,500**
#5 Clinical trial	#4 AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])	**175**
#6 Human only	#5 AND Humans filter	**144**
#7 English only	#6 AND English filter	**137**

2) Search Database: Embase

Search ID	Search Terms	Results
#1 Modulation	"rTMS" OR "tDCS" OR "tACS" OR "ta-VNS" OR "brain stimulation" OR "non-invasive neuromodulation" OR "non-invasive brain stimulation" OR "Transcranial Magnetic Stimulation" OR "Transcranial direct current stimulation" OR "transcranial alternating current stimulation" OR "Transcranial Direct Current Stimulation" OR "Transcranial Magnetic Stimulation" OR "Vagus Nerve Stimulation"	**116,337**
#2 Epilepsy	"Epilepsy" OR "seizures"	**363,382**
#3 Refractory	"Drug Resistant Epilepsy" OR "refractory" OR "drug resistant"	**370,136**
#4 Combine	#1 AND #2 AND #3	**4,334**
#5 Clinical trial	#4 AND ("randomized controlled trial" OR "controlled clinical trial")	**326**
#6 Human only	#5 AND "Human"	**320**
#7 English only	#6 AND [english]/lim	**309**
#8 Date	#6 AND Year Filter (2015 -2024)	**202 results**

3) Search Database: Scopus

Search ID	Search Terms	Results
#1 Modulation	"rTMS" OR "tDCS" OR "tACS" OR "ta-VNS" OR "brain stimulation" OR "non-invasive neuromodulation" OR "non-invasive brain stimulation" OR "Transcranial Magnetic Stimulation" OR **"**Transcranial direct current stimulation" OR "transcranial alternating current stimulation" OR "Transcranial Direct Current Stimulation" OR "Transcranial Magnetic Stimulation" OR "Vagus Nerve Stimulation"	**79,415**
#2 Epilepsy	"Epilepsy" OR "seizures"	**394,212**
#3 Refractory	"Drug Resistant Epilepsy" OR "refractory" OR "drug resistant"	**325,907**
#4 Combine	#1 AND #2 AND #3	**2,868**
#5 Clinical trial	#4 AND ("randomized controlled trial" OR "controlled clinical trial")	**308**
#6 Human only	#5 AND "Human"	**301**
#7 English only	#6 AND English language filter	**289**
#8 Date	#6 AND Year Filter (2015 -2024)	**191 results**