INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None.

Effect of vagus nerve stimulation for the treatment of drug-resistant epilepsy: a protocol of systematic review and meta-analysis

Chen, P[1]; Hao, MM[2]; Zhu, J[3]; Yang, ZY[4].

Review question / Objective: **Can vagus nerve stimulation (VNS) effectively treat drug-resistant epilepsy (DRE)?**
Condition being studied: **Drug-resistant epilepsy and vagus nerve stimulation.**
Information sources: **Electronic database searches The following electronic databases will be sought from the commencement up to the March 31, 2020 with no language and publication status restrictions: MEDILINE, EMBASE, Cochrane Library, Web of Science, PsycINFO, CINAHL, AMED, and China National Knowledge Infrastructure. We will include any RCTs that investigating the effect and safety of VNS for the treatment of patients with DRE. Take MEDILINE as an example, the specific search strategy is created. The similar search strategies will be modified and will be applied to the other electronic databases. Other resources searches Aside from above electronic databases, we will review and identify relevant review reference lists, conference abstracts, dissertations, and websites of clinical trials registry.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 April 2020 and was last updated on 15 April 2020 (registration number INPLASY202040086).

INTRODUCTION

Review question / Objective: **Can vagus nerve stimulation (VNS) effectively treat drug-resistant epilepsy (DRE)?**

Condition being studied: **Drug-resistant epilepsy and vagus nerve stimulation.**

METHODS

Participant or population: **We will consider all adult patients (18 years old or over) who were diagnosed as DRE. There is no restriction of race, gender, country, educational background and economic status.**

Intervention: This study will include trials that took VNS therapy as the alone treatment in the intervention group.

Comparator: The control group can use any management for patients with DRE. However, we will not consider combination therapy of VNS and any other therapies.

Study designs to be included: We will include randomized controlled trials (RCTs) of VNS therapy for patients with DRE.

Eligibility criteria: This will include RCTs of VNS vs. Other therapy for patients with DRE.

Information sources: Electronic database searches The following electronic databases will be sought from the commencement up to the March 31, 2020 with no language and publication status restrictions: MEDILINE, EMBASE, Cochrane Library, Web of Science, PsycINFO, CINAHL, AMED, and China National Knowledge Infrastructure. We will include any RCTs that investigating the effect and safety of VNS for the treatment of patients with DRE. Take MEDILINE as an example, the specific search strategy is created. The similar search strategies will be modified and will be applied to the other electronic databases. Other resources searches Aside from above electronic databases, we will review and identify relevant review reference lists, conference abstracts, dissertations, and websites of clinical trials registry.

Main outcome(s): The primary outcome is seizure freedom. It is defined as no seizures occur after the treatment within a period that equals to three times the longest pre-intervention inter-seizure interval over the previous year.

Additional outcome(s): Secondary outcomes are frequency of seizures (times/per week, or times/per month), quality of life (as measured by any validated scales based on the trial reported), all cause mortality, visits to the emergency room, and any expected or unexpected adverse events.

Data management: Two authors will independently collect data to fill out the pre-designed data extraction sheet. If any disagreements occur, a third author will be involved to settle down such issues through discussion. The extracted information consists of tile, first author, country, year of publication, methodological quality, patient characteristics, details of intervention and controls, outcomes, results and findings, follow-up, adverse events, funding sources, and conflict of interest.

Quality assessment / Risk of bias analysis: Based on the guideline of the Cochrane Handbook of Systematic Reviews of Interventions, two authors will independently assess the risk of bias for each included trial. We will appraise from 7 aspects, and each one will rate into 3 levels: low, unclear and high risk of bias. Any divergences between two authors will be solved by a third author through consultation.

Strategy of data synthesis: RevMan 5.3 software will be utilized to perform all data analysis and meta-analysis if it is possible. For continuous outcomes (e.g. seizure freedom, frequency of seizures, quality of life, visits to the emergency room), we will present them as mean difference or standardized mean difference with 95% confidence intervals (CIs). For dichotomous outcomes (e.g. all cause mortality, adverse events), we will calculate them as risk ratio and 95% CIs. We will use I^2 statistic to investigate the heterogeneity across the eligible trials. If the values of I^2 are $\leq 50\%$, reasonable heterogeneity will be considered, and a fixed-effects model will be employed. Meanwhile, we will undertake meta-analysis if sufficient similar studies in relation to the study information, participant characteristics, interventions, comparators, and outcomes. On the other hand, if the values of I^2 are $> 50\%$, substantial heterogeneity will be regarded, and a random-effect model will be exerted. At the same time, we will implement subgroup analysis to identify the possible sources for the significant heterogeneity.

Subgroup analysis: Subgroup analysis will be carried out based on the different types of interventions, comparators, and outcome measurements.

Sensibility analysis: We will undertake sensitivity analysis to assess the robustness of results by removing high risk of bias studies when significant heterogeneity exists.

Country(ies) involved: China.

Keywords: Drug-resistant epilepsy; vagus nerve stimulation; effect; safety.