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REVIEW ARTICLE

Adjunctive Vagus Nerve Stimulation for Treatment-Resistant Depression: a Quantitative Analysis

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Abstract

Vagus nerve stimulation (VNS) has been increasingly studied in treating treatment-resistant depression (TRD), but the findings have been mixed. This updated meta-analysis was conducted to examine the efficacy and safety of adjunctive VNS for TRD. Controlled studies reporting on the efficacy and safety of adjunctive VNS for TRD were screened, identified and analyzed. Standardized mean difference (SMD), risk ratio (RR) and their 95% confidence intervals (CIs) were analyzed using RevMan version 5.3. Three controlled studies with a total of 1048 patients with TRD compared VNS ($n = 622$) with control ($n = 426$) groups. Only one study was rated as 'high quality' using the Jadad scale. Adjunctive VNS was significantly superior to the control group regarding study-defined response [SMD:1.96 (95%CI:1.60, 2.40), $P < 0.00001$, $I^2 = 0\%$]. Patient-reported voice alteration occurred more frequently with adjunctive VNS for patients with TRD. No significant group differences were found regarding discontinuation due to any reason [RR:0.50 (95%CI:0.12, 2.09), $P = 0.34$, $I^2 = 85\%$]. Adjunctive VNS appeared to be effective and relatively safe treatment for TRD. Further randomized controlled trials are needed to confirm the efficacy and safety of VNS for TRD.

Keywords Vagus nerve stimulation · Treatment-resistant depression · Depressive symptoms · Safety · Meta-analysis

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Introduction

Major depressive disorder (MDD), as a common mental disorder worldwide, is associated with high rates of relapse and rehospitalization [1]. Despite advances in pharmacotherapy and psychotherapy, up to one-third patients with MDD who failed to response to more than two antidepressant trials of adequate doses and duration are considered as treatment-resistant depression (TRD) [2]. Augmentation strategies, such as antidepressants polypharmacy [3], adjunctive antipsychotics [4], antiepileptic drugs [5], ketamine [6–9], esketamine [10–13], anti-inflammatory drugs [14, 15], electroconvulsive therapy (ECT) [16], neuromodulation including repetitive transcranial magnetic stimulation (rTMS) [17], transcranial direct current stimulation (tDCS) [18] and vagus nerve stimulation (VNS) [19, 20] have been widely used in the treatment of TRD.

As a novel therapeutic neuromodulation technique, VNS comprises an implanted electrical pulse generator to stimulate the vagus nerve [21]. In 1997, the United States Food and Drug Administration (FDA) approved VNS for treatment of medically refractory seizures [21]. VNS was approved by FDA as an adjunct treatment for TRD in 2005 [22, 23]. Numerous case report/series [24–26] and observational studies [27–30] had found that adjunctive VNS was effective in improving depressive symptoms for patients with TRD, but its tolerability and safety remains mixed. Similarly, controlled studies [28, 31, 32] examined the effectiveness, safety and tolerability of VNS as an adjunct treatment for TRD with conflicting results.

To data, a growing number of systematic reviews and meta-analyses had been conducted to examine the effectiveness, safety and tolerability of VNS as an adjunct treatment for TRD [19, 20, 23, 33–35], but with inconsistent findings. For examine, a patient-level meta-analysis found that the combination of VNS and treatment as usual (TAU) group was associated with greater response and remission rates when compared to the TAU group [23]. However, the latest meta-analysis including only two randomized controlled trials (RCTs) ($n = 134$) found no significant difference on improvement percentage of Hamilton Depression Rating Scale (HAMD) and Montgomery–Asberg depression rating scale (MARDS) between adjunctive VNS group and the control group [34]. Importantly, one study [36] on auricular transcutaneous electrical nerve stimulation was included by the Lv et al's meta-analysis [34], which have heterogeneous effects. Thus, an updated meta-analysis of controlled studies was performed in order to assess the effectiveness, safety and tolerability of VNS as an adjunct treatment for TRD.

Methods

Search Strategy

In accordance with the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [37], we performed this systematic review and meta-analysis. Two independent investigators (XZ and YHR) searched Chinese (WanFang and Chinese Journal Net) and English (EMBASE, PsycINFO, PubMed, and Cochrane Library) databases from inception to Dec 3, 2019 using the following search terms: ("vagus nerve stimulation"[Mesh] OR "vagus nerve stimulation" OR VNS OR "vagal nerve stimulation") AND ("depression"[Mesh] OR melancholia OR depressed OR depressive OR depression). Moreover, the bibliographies of eligible controlled studies [28, 31, 32] and relevant reviews [19, 20, 23, 33, 34] were manually checked by the same two investigators for additional studies.

Study Criteria

The inclusion criteria of this study were in line with the ***PICOS*** strategy according to the Cochrane Collaboration [38] as follows: ***P***articipants: adult patients diagnosed with TRD according to international diagnostic criteria. ***I***ntervention: VNS plus TAU. ***C***omparison: TAU monotherapy. ***O***utcomes: the primary outcome was study-defined response and remission at post-VNS treatment; Key secondary outcomes included: (1) the improvement of depressive symptoms at post-VNS treatment as measured using standardized rating scales [such as the MARDS [39, 40] or HAMD [41, 42]]; (2) rate of discontinuation; (3) rate of patient-reported adverse events. ***S***tudy design: controlled studies investigated VNS treatment for improvement of depressive symptoms that were evaluated using either the HAMD or MARDS in TRD patients.

Data Extraction

Two independent investigators (XZ and YHR) extracted data to avoid extraction errors, resolving inconsistencies by consensus or a discussion with a senior investigator (YMG). The following parameters were extracted from each included RCT: study characteristic (such as the first author, publication year, and country of origin), basic demographic and clinical data (such as sample size, illness duration, VNS treatment parameters, mean age, etc), and measurement outcomes (such as therapeutic effectiveness, tolerability and safety of VNS treatment). The first/correspondent authors were contacted by emails or telephones in order to obtain additional information if necessary. If more than one study were published on the same dataset [31, 43, 44], only the one with the most complete data was included [31].

Data was extracted by two independent investigators (XZ and YHR) from the graphs or figures of the included trials using the WebPlotDigitizer 4.1 version (https://automeris.io/WebPlotDigitizer/). In Aaronson et al's study [31], the whole trial duration was 5 years; only data until to 12 months were extracted to reduce the heterogeneity of the studies as recommended by prior meta-analysis [45].

Statistical Methods

Data were synthesized using RevMan version 5.3 with a random-effects model [46]. Dichotomous (such as rate of study defined response or remission) and continuous (such as score assessments using HAMD or MARDS) data were synthesized by risk ratio (RR) and standardized mean difference (SMD) with their 95% confidence interval (CI), respectively. All meta-analyses were considered statistically significant at the level of $P < 0.05$. The heterogeneity across studies was detected using the Q-test and the I^2 statistic, with $P < 0.10$ and $I^2 \geq 50\%$ suggesting the significance of heterogeneity [47]. In this meta-analysis, in case of $I^2 \geq 50\%$ for primary outcome, sensitive, subgroup and meta-regression analyses would be examined to investigate the source of heterogeneity, if possible. The publication bias was estimated by visual funnel plots and Egger's test [48], with a $P < 0.05$ being considered significant.

The Assessment of Study Quality

The Cochrane risk of bias [38] and the Jadad scale [49] were used by two independent investigators (XZ and YHR) to assess the quality of each included study. Disagreements were

resolved by consensus or a discussion with a senior investigator (YMG). The Jadad total score more than 3 points was considered as "high quality" [50].

Results

Literature Search

In total, 3059 hits were identified: 3058 by database search and 1 by hand search (Fig. 1). Three studies [31, 43, 44] with overlapping data were published, only Aaronson et al's study [31] with the most complete data was included. Similarly, in the two studies [28, 51] with overlapping data, only Rush et al's study [28] was included. Finally, 3 controlled studies [28, 31, 32] were included and meta-analyzed.

Study Characteristics

Three studies with 1048 patients with TRD compared VNS ($n = 622$) with control ($n = 426$) groups (Table 1). One study was conducted in USA and Canada ($n = 235$), and one each in USA ($n = 795$) and Germany ($n = 18$). The weighted mean age was 48.7 (range = 46.5 to 50.1) years and the weighted illness duration was 24.2 (range = 7.1 to 25.5) years in 2 studies with

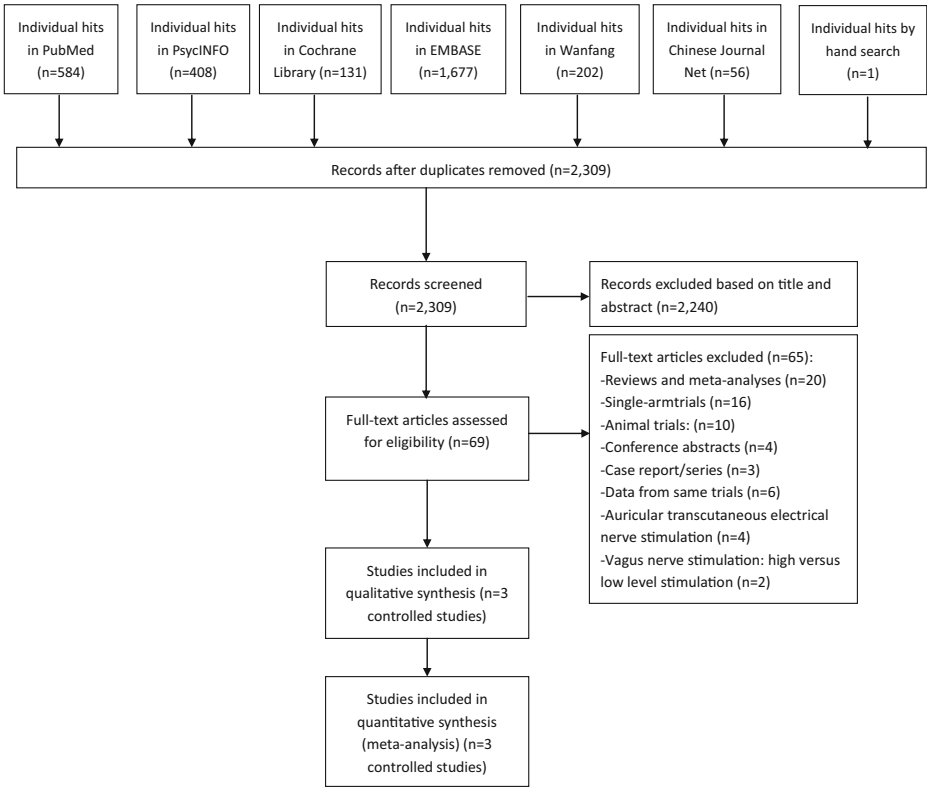

Fig. 1 PRISMA flow diagram

Table 1 Summary of studies included in this meta-analysis

Study (country)	*N*	Design: -Blinding	Participants: -Criteria -Illness duration (yrs)	Sex[a]: Male (%)	Age[a]: yrs (range)	Invention and control groups; number of patients	Dose of VNS	Treatment duration	Number of prior MDEs	Resistance definition (Failure of)	Jadad score
Rush et al. 2005 (USA & Canada)	235	-Double blind	-DSM-IV -TRD -25.5	159 (71.6)	46.5 (24–72)	a. active VNS + TAU; *n* = 119 b. sham VNS + TAU; *n* = 116	20 Hz, 500 μs pulse width, and on/off cycle of 30 s on and 5 min off during the 2-week stimulation adjustment and acute phase trial period. The output current, beginning at 25 mA as the lowest dose, was increased gradually (in 25 mA increments) until a comfortable level was reached.	12 weeks	≥ 4 (including current)	≥ 2 but ≤6	5
Aaronson et al. 2017 (USA)[b]	795	-Non-randomized comparative studies	-DSM-IV-TR -TRD -NR	234 (29.4)	49.3 (>18)	a. VNS + TAU; *n* = 494 *b. TAU*; *n* = 301	NR	5 years	≥ 3 (including current)	≥ 4 (Including ECT)	1
Sperling et al. 2009 (Germany)	18	- Non-randomized comparative studies	-DSM-IV -TRD -7.1	8 (44.4)	50.1 (NR)	a. VNS + TAU; *n* = 9 b. TAU; n = 9	VNS doses adjustments measured each time 0.25–2.5 mA stimulation strength at 15–30 Hz frequency, allowing for the usual on times (30 s) and off times (5 min stimulation-free interval).	12 months	Unclear	Mean = 4 per group	1

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders4th edition, Text Revision, *ECT* electroconvulsive therapy, *MDEs* Major Depressive Episodes, *NR* not report, *VNS* vagus nerve stimulation, *TAU* treatment as usual, *TRD* treatment refractory depression, *yrs.* years

[a] Available data were extracted based on mean baseline value of each included trials

[b] The whole trial duration was 5 years; only data until to 12 months were extracted to reduce the heterogeneity of the studies

available data. All participants had a diagnosis of TRD and resistance definitions included failure of treatment with ≥2 ADs (1 study) and ≥4 ADs (2 studies).

Study Quality Assessment

In two studies [31, 32] subjects were not randomized; the remaining one RCT [28] with double blinded design described an adequate method of random sequence generation (Supplemental Figure 2). The weighted Jadad score was 1.9 (range = 1 to 5), and only one study [28] was rated as 'high quality' (Table 1).

Response and Remission

Meta-analysis of study-defined response [SMD:1.96 (95%CI:1.60, 2.40), $P < 0.00001$, $I^2 = 0\%$, Fig. 2] found that adjunctive VNS was significantly superior to the control group. Only one study [31] reported the rate of remission, finding an advantage of adjunctive VNS over the control group.

Two-thirds of the included studies reported the changes of depressive symptoms as measured by HAMD and/or MADRS. One study found that adjunctive VNS was associated with the improvement of depressive symptoms as measured by HAMD [32], but another study found no group differences regarding HAMD and MARDS improvement from baseline [28].

Adverse Events and Discontinuation

Two-thirds of the included studies examined the adverse events of VNS for TRD (Supplemental Table 1), but the data collected by using different instruments were not meta-analyzable. Rush et al. found the most common adverse events of VNS was voice alteration [28].

Meta-analyses of discontinuation due to any reason found no significant difference between the two group [RR:0.50 (95%CI:0.12, 2.09), $P = 0.34$, $I^2 = 85\%$, Fig. 3].

Publication Bias

Due to the small numbers ($n < 10$) of included controlled studies, publication bias could not be detected [52].

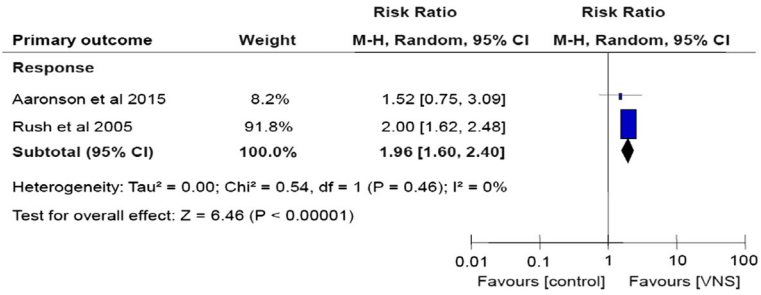

Fig. 2 Adjunctive vagus nerve stimulation for treatment-resistant depression: Forest plot of study-defined response

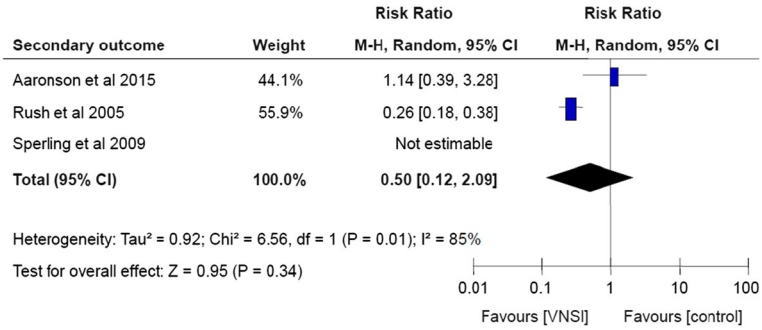

Fig. 3 Adjunctive vagus nerve stimulation for treatment-resistant depression: Forest plot of study-defined discontinuation due to any reason

Discussion

This updated meta-analysis of three controlled studies with 1048 patients with TRD found that adjunctive VNS has greater rate of response than the control group. This adjunctive strategy appears to be safe and tolerability. A case report found that VNS therapy was effective and safe for patients with TRD during pregnancy and delivery [53]. Given that only one RCT [28] included in this meta-analysis, these findings need to be interpreted with caution. Sackeim et al. found VNS in TRD may result in enhanced neurocognitive function [54], but all included studies of this meta-analysis did not examine the neurocognitive effect of VNS for patients with TRD.

In addition to the antidepressant effect of VNS, it appeared to solve the problem of compliance that is commonly associated with regular treatments. Furthermore, other augmentation strategies including antidepressant polypharmacy or adjunctive antipsychotics could lead to significant ADRs, such as sexual dysfunction and metabolic abnormalities [55–57]. ECT had rapid antidepressant effect in TRD, but memory impairment and other adverse neurocognitive effects limited its use as a long-term therapy for TRD [33]. VNS had no deleterious neurocognitive effects and avoided the problem of systematic anaesthesia practiced in ECT [16]. An interesting study explored the use of ECT in the pivotal study of VNS for TRD, finding that administration of ECT did not affect the implanted VNS device [58].

The antidepressant effect of VNS is consistent with several observational studies [27, 29]. For example, Rush et al. found a 50% response rate (i.e., 50% reduction in MARDS scores) among outpatients with TRD after 10 weeks of VNS [27]. The antidepressant mechanisms of action of VNS could be attributed to its modulating role on the concentrations of neurotransmitters, such as gamma-aminobutyric acid (GABA), norepinephrine (NE), serotonin (5-HT) and glutamate, involving in the pathophysiology of MDD [59, 60]. Furthermore, if patients suffering from TRD had abnormalities in brain regions that were associated with the function of vagus nerve (i.e., "top-down" regulation), then VNS theoretically resulted in the normalization of activity in this dysfunctional circuit (i.e., a "bottom-up" approach) [61].

The recent meta-analysis [34] with 2 studies ($n = 255$) [28, 36] found no significant antidepressant effect of VNS, which is contrary to our findings. The possible reason could attribute to one study [36] on auricular transcutaneous electrical nerve stimulation included in Lv et al's meta-analysis [34], which could lead to a heterogeneous sample. In our study, two more controlled studies [31, 32] were included, potentially increasing our confidence for meta-analytic results. Furthermore, unlike the prior meta-analysis [34], the evaluation of study quality using Jadad scale [49] was included in this meta-analysis.

The findings of this meta-analysis should be interpreted with caution due to the following limitations. First, although broad study entry criteria were used, only 3 controlled studies were included, which limits more comprehensive analyses (i.e., publication bias or meta-regression analysis). Second, the data on remission was reported only in one study [31]. Third, two-thirds of the included studies were classified as 'low quality' using the Jadad scale [49], but low-quality evidence could still result in strong recommendations [62]. Finally, the cost-effectiveness of VNS in a long-term treatment of patients with TRD is still unknown.

In conclusion, VNS as an adjunct treatment appears to be effective, relatively safe and generally well tolerated in treating patients with TRD. Future large RCTs are needed to confirm the positive effects of adjunctive VNS for TRD.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest concerning this article.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent NA.

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