

## ORIGINAL ARTICLE

# Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: A meta-analysis

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**Objectives:** Lennox-Gastaut syndrome (LGS) is among the most severe epileptic and developmental encephalopathies. A meta-analysis was performed to evaluate the effectiveness of adjunctive vagus nerve stimulation (VNS Therapy) in patients with LGS.

**Materials & Methods:** PubMed database was queried (January 1997 to September 2018) to identify publications reporting on the efficacy of VNS Therapy in patients with LGS, with or without safety findings. Primary endpoint of the meta-analysis was the proportion of responders ( $\geq 50\%$  reduction in seizure frequency). Random-effects analysis was used to calculate weighted mean estimates and confidence intervals. Heterogeneity was evaluated by statistical tests including  $I^2$ .

**Results:** Of 2752 citations reviewed, 17 articles (480 patients) were eligible including 10 retrospective studies and seven prospective studies. A random-effects model produced a pooled proportion of 54% (95% confidence intervals [CI]: 45%, 64%) of patients with LGS who responded to adjunctive VNS Therapy ( $p$  for heterogeneity  $< 0.001$ ,  $I^2 = 72.9\%$ ). Per an exploratory analysis, the calculated incidence of serious adverse events associated with VNS Therapy was 9% (95% CI: 5%, 14%); the rate was higher than in long-term efficacy studies of heterogeneous cohorts with drug-resistant epilepsy and likely attributed to variable definitions of serious adverse events across studies.

**Conclusions:** The meta-analysis of 480 patients with LGS suggests that 54% of patients responded to adjunctive VNS Therapy and that the treatment option was safe and well-tolerated. The response in patients with LGS was comparable to heterogeneous drug-resistant epilepsy populations. A clinical and surgical overview has been included to facilitate the use of VNS in LGS.

## KEYWORDS

epilepsy, Lennox-Gastaut syndrome, seizures, systematic meta-analysis review, vagus nerve stimulation

## 1 | INTRODUCTION

Lennox-Gastaut syndrome (LGS) is among the most severe epileptic and developmental encephalopathies. LGS arises in childhood with an onset between 18 months and 8 years of age, and most often

between 3 and 5 years of age.<sup>1</sup> LGS accounts for about 3% to 5% of all childhood epilepsies.<sup>2,3</sup>

LGS is characterized by the occurrence of multiple drug-resistant seizure types, characteristic slow spike-and-wave electroencephalogram activity, and usually cognitive impairment and behavioral

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problems. LGS poses a therapeutic challenge, and optimal management requires complex antiepileptic treatment strategies while balancing the side effects of medications and attempting to preserve cognitive function.<sup>1</sup> Complete seizure control is rarely seen; the resolution of intellectual and psychosocial dysfunction is often not feasible. Notably, patients with LGS who received adequate treatment very early in their disease process have been documented to have a more favorable overall outcome.<sup>4,5</sup>

VNS Therapy is indicated for use as an adjunctive neuromodulatory therapy for reducing the frequency and severity of seizures in patients with drug-resistant epilepsy. In Europe, VNS Therapy is approved for use in patients of all ages whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. In the United States, VNS Therapy is approved in patients who are 4 years of age and older with focal onset seizures.

Several studies have evaluated the safety and efficacy of VNS Therapy in the treatment of LGS.<sup>6–10</sup> Based on a pooled analysis of adjunctive VNS Therapy, about 55% of patients with LGS achieved >50% reduction in seizure frequency at one to ten years after implantation.<sup>6,9,11–13</sup> In this meta-analysis, we examined the clinical effectiveness of adjunctive VNS Therapy in the treatment of seizures in patients with LGS, by analyzing seizure frequency changes after VNS Therapy in patients with LGS reported in the literature. We have also provided a clinical and surgical overview to facilitate understanding of the use of VNS Therapy in the treatment of patients with LGS.

## 2 | METHODS

### 2.1 | Search strategy and selection criteria

The present meta-analysis was modeled after the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and adheres to a structured review protocol not pre-registered in an International Prospective Register for systematic reviews. A systematic search of the electronic PubMed database of the United States National Library of Medicine at the National Institutes of Health was performed from January 1997 to September 2018 to identify published peer-reviewed original research studies that reported on efficacy of VNS Therapy in patients with LGS, with or without safety findings. There were no restrictions on study design. No language restrictions were applied during the search of the PubMed database and the search terms included combinations of (a) VNS, vagal nerve stimulation, vagus nerve stimulation, and (b) Lennox-Gastaut, LGS. A thorough review of the abstracts from the identified articles was independently conducted by two independent reviewers (MD and MAK). The reviewers evaluated the quality assessments of the eligible clinical studies and assessed the likelihood of bias; any discordances in the selection process were resolved by consensus and/or additional referees. Duplicate reporting was excluded from the analyses. The complete full-text versions of the remaining articles

were then reviewed by both reviewers to yield the final pool of articles included in this analysis.

### 2.2 | Data extraction

Baseline, procedural, and outcome data were independently abstracted by the two reviewers (MD and MAK). Specifically, potential sources of significant clinical heterogeneity, such as study design, single center or multicenter, sample size, and follow-up duration, as well as primary study endpoints and other key outcomes, have been captured in a data extraction table (available from the authors upon request).

### 2.3 | Analysis endpoints

The primary endpoint for the meta-analysis was the proportion of responders who reported  $\geq 50\%$  reduction in seizure frequency at the longest available follow-up period during treatment with adjunctive VNS Therapy. Proportion of serious and mild transient adverse events were evaluated as exploratory endpoints.

### 2.4 | Statistical analysis

A random-effects meta-analysis was performed to combine study-specific estimates and to calculate the correspondent weighted mean estimate of proportion of responders ( $\geq 50\%$  reduction in seizure frequency) for patients with LGS treated with VNS Therapy.

Each pooled estimate was derived by interpolating a random-effects model which accommodates the presence of clinical, methodological, and statistical heterogeneity. A restricted maximum-likelihood estimator was used to estimate the between-studies variance. Fixed-effect model was used as sensitivity analysis to confirm the results related to the primary endpoint.

All analyses were conducted using the Freeman-Tukey double arcsine transformation of the study-specific proportions<sup>14</sup> to stabilize the estimate's variance and to make the normal distribution assumptions more applicable to significance testing. This allowed the inclusion of studies with proportions equal to 0 or 100% and avoided confidence intervals exceeding the 0 to 1 range. Thereby, studies with 0 events or 100% events will contribute to the pooled estimate without the use of continuity corrections.

Overall estimates, and the correspondent 95% confidence intervals, were derived from proportion of back-transformations which were calculated applying the formula  $p = \sin(2t/2)^2$ , where  $t$  represents the Freeman-Tukey double arcsine of the overall or confidence limits estimates.<sup>15</sup>

Potential publication bias on transformed proportions of responder was analyzed using Begg-Mazumdar's rank correlation test and the Egger's linear regression test.<sup>16,17</sup> Univariate meta-regression analyses and stratified meta-analyses were performed to explore the relation between study-specific-transformed proportions

of responder and year of publication, longest follow-up available, and study design.

Studies included in the meta-analysis were graphically displayed by means of forest plots; heterogeneity across studies were assessed using Cochran's Q statistics, and the extent of statistical consistency was measured with Higgins and Thompson  $I^2$  statistics.

Exploratory analysis was performed on the number of participants with serious adverse events and mild transient adverse events and analyzed based on means of a random-effects model.

Statistical significance was set at the two tailed 0.05 level for publication bias and meta-regression coefficients, whereas a 0.10 statistical significance was used for heterogeneity.

### 3 | RESULTS

#### 3.1 | Eligible articles

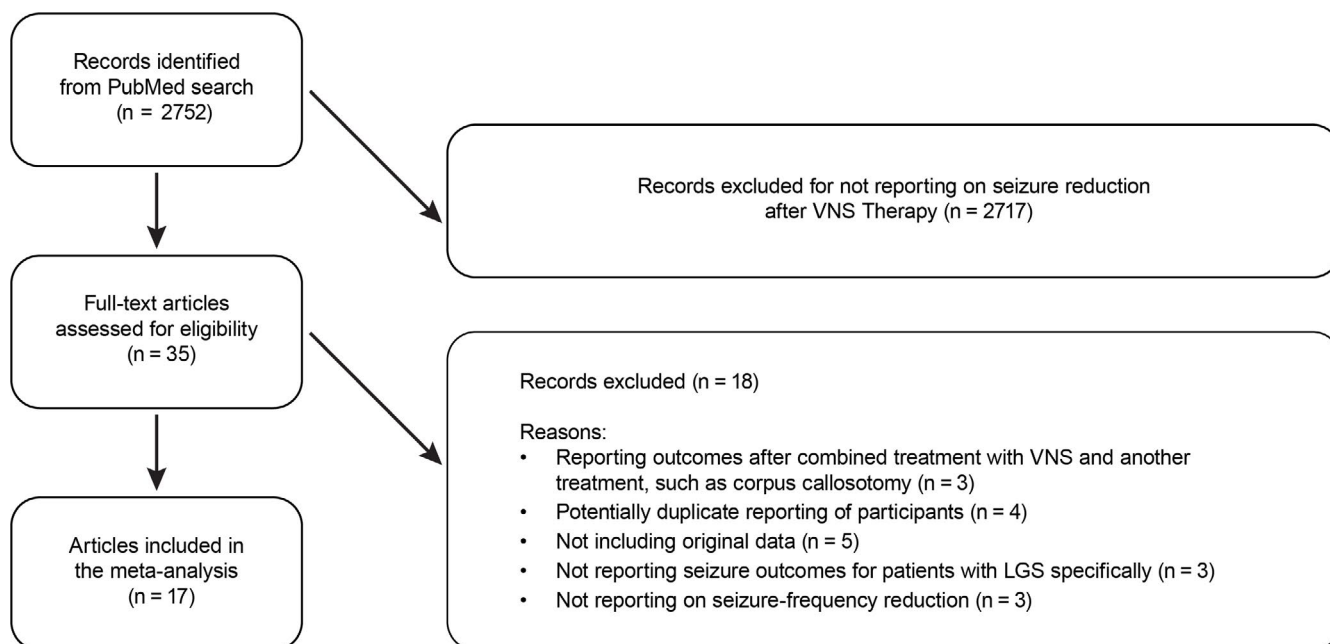
The original literature search identified 2752 abstracts (Figure 1). Of these, 2717 were excluded as they were not relevant (ie, not reporting on seizure reduction after VNS Therapy in patients with LGS), leaving 35 to be examined at full text. Among these, 18 records were excluded for one or more of the following reasons: reporting of outcomes after combined treatment with VNS and another treatment (eg, corpus callosotomy); potentially duplicate reporting of participants; not including original data; not reporting seizure outcomes for patients with LGS specifically; and for not reporting on seizure frequency reduction.

The remaining 17 articles reporting original data on seizure frequency in 480 patients with LGS who were treated with VNS Therapy were included in this meta-analysis (Table 1).<sup>7-10,12,18-29</sup> The studies were categorized based on their prospective or retrospective design. One of the articles (Buoni et al.) was conservatively categorized as a retrospective study as it was not possible to conclusively ascertain whether had a prospective or retrospective design.<sup>21</sup> As such, 10 of the studies were retrospective and seven of the studies were conducted prospectively. The included studies were published between May 1997 and May 2016. One study received partial support from the device manufacturer,<sup>24</sup> and one study was sponsored by the device manufacturer.<sup>10</sup>

#### 3.2 | Proportion of responders and sensitivity analyses

The pooled proportion (back transformation) of responders (271 out of 480 participants) produced an estimate of 54% (95% CI: 45%, 64%) of patients with LGS who responded to adjunctive VNS Therapy; proportion = 0.54; 95% CI: 0.45, 0.64;  $I^2 = 72.9%$ ; Q  $p$ -value for heterogeneity <0.001, based on the random-effects model with inclusion of the 17 identified studies (Figure 2).

To assess sensitivity, the mean estimates from pooled proportions across studies and 95% confidence intervals were calculated based on both the random-effects model and the fixed-effect model (Table S1).



**FIGURE 1** PRISMA diagram showing the numbers of abstracts that were identified, examined at full text, and included in the final meta-analysis. Of the 2752 abstracts identified in the original search on the effects of VNS Therapy in patients with LGS, 2717 abstracts were excluded for not reporting on seizure reduction after VNS Therapy. The remaining 35 articles were examined at full text, and among these, 18 records were excluded for reasons listed in the diagram, and the remaining 17 articles were included in the meta-analysis

TABLE 1 Baseline characteristics of patients in the 17 studies included in the meta-analysis

| Author, year                           | Study center   | Characteristics of study participants with Lennox-Gastaut syndrome   |
|--|--|--|
| Aldenkamp et al, 2002 <sup>19</sup>    | Single center in the Netherlands; prospective design                         | <ul style="list-style-type: none"> <li>• Number of participants: 19</li> <li>• Sex: 21% female</li> <li>• Age at seizure onset: Mean of 2 years 7 months (range, 0–8 years)</li> <li>• Known disease etiology include perinatal anoxia (<math>n = 4</math>), dysplasia (<math>n = 2</math>), and viral meningoencephalitis (<math>n = 1</math>)</li> <li>• Duration of epilepsy prior to VNS implant: 8 years 6 months</li> <li>• Number of participants with prior corpus callosotomy: 0</li> <li>• Age at VNS device implantation: Mean of 11 years 2 months (range, 6 years–19 years)</li> <li>• Follow-up after VNS implant: 2 years</li> <li>• Number of responders: 4</li> </ul>   |
| Ben-Menachem et al, 1999 <sup>20</sup> | Single center in Sweden; prospective design                                  | <ul style="list-style-type: none"> <li>• Number of participants: 8</li> <li>• Age: Unknown</li> <li>• Seizure types: generalized tonic-clonic seizures, absence seizures, and atonic seizures</li> <li>• Number of participants with prior corpus callosotomy: 5</li> <li>• Follow-up after VNS implant: Mean of 20 months (range, 3 months–5 years 4 months)</li> <li>• Number of responders: 5</li> </ul>  |
| Buoni et al, 2004 <sup>21</sup>        | Single center in Italy from May 1999 to May 2002; prospective design         | <ul style="list-style-type: none"> <li>• Number of participants: 7</li> <li>• Sex: 43% female</li> <li>• Age range at seizure onset: 2 days–12 years</li> <li>• Severe mental retardation: <math>n = 5</math></li> <li>• Known disease etiology: Prenatal rubella (<math>n = 1</math>), neurofibromatosis type 1 (<math>n = 1</math>), measles encephalopathy (<math>n = 1</math>), complex cerebral malformation (<math>n = 1</math>), and post-radiotherapy encephalopathy (<math>n = 1</math>)</li> <li>• Seizure types: Atonic seizure, atypical absence, complex partial seizure, general tonic-clonic seizure (GTCS), myoclonic seizure,</li> <li>• Number of participants with prior corpus callosotomy: 0</li> <li>• Duration of epilepsy prior to VNS implant: mean of 13 years (range, 9–19 years)</li> <li>• Age at VNS device implant: Mean of 19 years (range, 15–28 years)</li> <li>• Follow-up after VNS implant: Mean of 22 months (range, 9 months–3 years)</li> <li>• Number of responders: 3</li> </ul> |
| Casazza et al, 2006 <sup>22</sup>      | Single center in Italy from October 1995 to October 2000; prospective design | <ul style="list-style-type: none"> <li>• Number of participants: 4</li> <li>• Sex: 50% female</li> <li>• Mean age at seizure onset: 3 years 6 months (4 months–8 years)</li> <li>• Disease etiology: Unknown (<math>n = 2</math>), perinatal injury (<math>n = 1</math>), and complex cerebral malformation (<math>n = 1</math>)</li> <li>• Number of participants with prior corpus callosotomy: 0</li> <li>• Follow-up after VNS implant: 4–9 years</li> <li>• Number of responders: 0</li> </ul>  |
| Cersosimo et al, 2011 <sup>23</sup>    | Single center in Italy; prior to 2010; retrospective design                  | <ul style="list-style-type: none"> <li>• Number of participants: 46</li> <li>• Sex: 43% female</li> <li>• Severe mental retardation: <math>n = 7</math></li> <li>• Mean duration of epilepsy prior to VNS implant: 10 years 6 months</li> <li>• Approximate age at VNS device implantation: 13 years (range, 5–20 years)</li> <li>• Follow-up after VNS implant: Mean of 2 years 6 months (range, 1–9 years)</li> <li>• Number of responders: 30</li> </ul>  |
| Cukiert et al, 2013 <sup>18</sup>      | Single center in Brazil; implanted from 2008–2009; prospective design        | <ul style="list-style-type: none"> <li>• Number of participants: 20</li> <li>• Follow-up after VNS implant: 2 years</li> <li>• Number of responders: 17</li> </ul>   |

(Continues)

TABLE 1 (Continued)

| Author, year                       | Study center  | Characteristics of study participants with Lennox-Gastaut syndrome  |
|------------------------------------|---|---|
| Frost et al, 2001 <sup>8</sup>     | Six centers in the United States; implanted before December 1998; retrospective design    | <ul style="list-style-type: none"> <li>• Number of participants: 24</li> <li>• Follow-up after VNS implant: 6 months</li> <li>• Number of responders: 14</li> </ul>   |
| Hornig et al, 1997 <sup>24</sup>   | Single center in the United States; prospective design                                    | <ul style="list-style-type: none"> <li>• Number of participants: 6</li> <li>• Known disease etiology: Cryptogenic</li> <li>• Number of participants with prior corpus callosotomy: 4</li> <li>• Age at VNS device implantation: Mean of 9 years (range, 6–13 years)</li> <li>• Follow-up after VNS implant: 2 months–2 years 6 months</li> <li>• Number of responders: 5</li> </ul>   |
| Hosain et al, 2000 <sup>25</sup>   | Single center in the United States; study dates are unknown; prospective design           | <ul style="list-style-type: none"> <li>• Number of participants: 13</li> <li>• Sex: 23% female</li> <li>• Mean age at seizure onset:</li> <li>• Seizure types: Tonic, atonic, atypical absence, myoclonic, generalized tonic-clonic, or complex partial</li> <li>• Number of participants with prior corpus callosotomy: 3</li> <li>• Age at VNS device implantation: Mean of 16 years (range, 4–44 years)</li> <li>• Follow-up after VNS implant: &gt;6 months</li> <li>• Number of responders: 6</li> </ul>   |
| Karczeski et al, 2001 <sup>7</sup> | Data from VNS patient registry; data collected prior to April 2001; retrospective design  | <ul style="list-style-type: none"> <li>• Number of participants: 167</li> <li>• Number of participants with prior corpus callosotomy: 23</li> <li>• Follow-up after VNS implant: 1 year 6 months</li> <li>• Number of responders: 107</li> </ul>  |
| Katagiri et al, 2016 <sup>26</sup> | Single center in Japan; implanted from January 2012–April 2014; retrospective study       | <ul style="list-style-type: none"> <li>• Number of participants: 10</li> <li>• Sex: 60% female</li> <li>• Age at seizure onset: 13 months (range, 1–37 months)</li> <li>• Number of participants with prior corpus callosotomy: 10</li> <li>• Age at VNS device implantation: Mean of 10 years 8 months (range, 3–30 years)</li> <li>• Follow-up after VNS implant: 1 year</li> <li>• Number of responders: 6</li> </ul>  |
| Kostov et al, 2009 <sup>12</sup>   | Single center in Norway; implanted from 1997–2007; retrospective design                   | <ul style="list-style-type: none"> <li>• Number of participants: 30</li> <li>• Sex: 43% female</li> <li>• Age at seizure onset: median of 1 year 1 month (range, 1 month–7 years)</li> <li>• Known disease etiology: Perinatal asphyxia (<i>n</i> = 7), cortical malformation (<i>n</i> = 5), lissencephaly (<i>n</i> = 2), corpus callosum agenesis (<i>n</i> = 2), meningoencephalitis (<i>n</i> = 2), and tuberous sclerosis (<i>n</i> = 1)</li> <li>• Number of participants with prior corpus callosotomy: 2</li> <li>• Duration of epilepsy prior to VNS implant: Median of 12 years</li> <li>• Age at VNS device implantation: Median of 13 years (range, 4–52 years)</li> <li>• Follow-up after VNS implant: Median of 4 years 4 months (range, 1 year 5 months–10 years 3 months)</li> <li>• Number of responders: 20</li> </ul> |
| Mikati et al, 2009 <sup>27</sup>   | Single center in Lebanon; implanted from August 2003 to November 2007; prospective design | <ul style="list-style-type: none"> <li>• Number of participants: 6</li> <li>• Sex: 67% female</li> <li>• Age at seizure onset: mean of 5 years 1 month (range, 9 months–9 years)</li> <li>• Known disease etiology: Cryptogenic</li> <li>• Seizure types: Generalized, atonic, absence, generalized tonic-clonic, and myoclonic</li> <li>• Number of participants with prior corpus callosotomy: Unknown</li> <li>• Age at VNS device implant: Mean of 23 years (range, 11–38 years)</li> <li>• Follow-up after VNS implant: 1 year 11 months (range, 8 months–3 years 11 months)</li> <li>• Number of responders: 3</li> </ul>   |

(Continues)

TABLE 1 (Continued)

| Author, year                      | Study center  | Characteristics of study participants with Lennox-Gastaut syndrome   |
|-----------------------------------|---|--|
| Orosz et al, 2014 <sup>10</sup>   | Multiple centers in the European Union; retrospective design                                  | <ul style="list-style-type: none"> <li>• Number of participants: 87</li> <li>• Sex: ~47% female</li> <li>• Age at seizure onset: Range, 1 month–9 years 6 months</li> <li>• Age at VNS device implantation: Range, approximately 2–18 years</li> <li>• Follow-up after VNS implant: 2 years</li> <li>• Number of responders: 34</li> </ul>   |
| Shahwan et al, 2009 <sup>28</sup> | Single center in Australia; implanted from August 1998 to August 2006; retrospective design   | <ul style="list-style-type: none"> <li>• Number of participants: 9</li> <li>• Disease etiology: Cryptogenic (<math>n = 5</math>), tuberous sclerosis (<math>n = 2</math>), lissencephaly (<math>n = 1</math>), and B12 deficiency (<math>n = 1</math>)</li> <li>• Seizure types: Tonic drops, tonic-clonic, status epilepticus; spasms</li> <li>• Age at VNS device implant: Mean of 10 years 6 months (range, 4 years 6 months–15 years 4 months)</li> <li>• Follow-up after VNS implant: 3 years 10 months (range, 1 year 10 months–8 years 6 months)</li> <li>• Number of responders: 7</li> </ul>                |
| You et al, 2008 <sup>9</sup>      | Multiple centers in South Korea; implanted between July 1995–March 2005; retrospective design | <ul style="list-style-type: none"> <li>• Number of participants: 10</li> <li>• Sex: 60% female</li> <li>• Age at seizure onset: 2 years (range, 1 month–8 years 2 months)</li> <li>• Seizure types: Tonic or atonic head-drop, myoclonic, generalized tonic, and generalized tonic-clonic</li> <li>• Number of participants with prior corpus callosotomy: 0</li> <li>• Duration of epilepsy prior to VNS implant: 8 years 8 months (range, 1 year 4 months–17 years 10 months)</li> <li>• Follow-up after VNS implant: 2 years 10 months (range, 1–6 years 11 months)</li> <li>• Number of responders: 7</li> </ul> |
| Zamponi et al, 2011 <sup>29</sup> | Single center in Italy; data collected from 2000–2008; retrospective design                   | <ul style="list-style-type: none"> <li>• Number of participants: 14</li> <li>• Sex: 29% female</li> <li>• Disease etiology: Cryptogenic (<math>n = 10</math>) and perinatal anoxia (<math>n = 3</math>)</li> <li>• Seizure types: Drop attacks, generalized, tonic, spasms, partial, and myoclonic</li> <li>• Number of participants with prior corpus callosotomy: 0</li> <li>• Age at VNS device implantation: Mean of 13 years 10 months (range, 5 years 5 months–25 years)</li> <li>• Follow-up after VNS implant: 3 years (range, 3–8 years 2 months)</li> <li>• Number of responders: 3</li> </ul>             |

VNS, Vagus Nerve Stimulation.

### 3.3 | Evaluation of publication bias

A funnel plot was generated—based on Freeman-Tukey double arcsine transformation of study-specific proportions—to assess publication bias of the estimate response rate. For the response rate, the asymmetry in the funnel plot was minimal (Figure S1). The absence of publication bias on responder proportions was further confirmed by the Begg-Mazumdar's rank correlation test (Kendall's tau =  $-0.07$ ,  $p$ -value =  $0.7$ ) and the Egger's linear regression test (regression coefficient =  $-0.67$  [95% CI  $-2.65$ ,  $1.32$ ],  $p$ -value =  $0.5$ ).

Stratified meta-analyses were performed to provide an estimate of the proportion of responders by retrospective or prospective design. Table S2 shows the results based on the random-effects model to calculate mean estimates from pooled proportions (back transformation) across the studies with retrospective versus

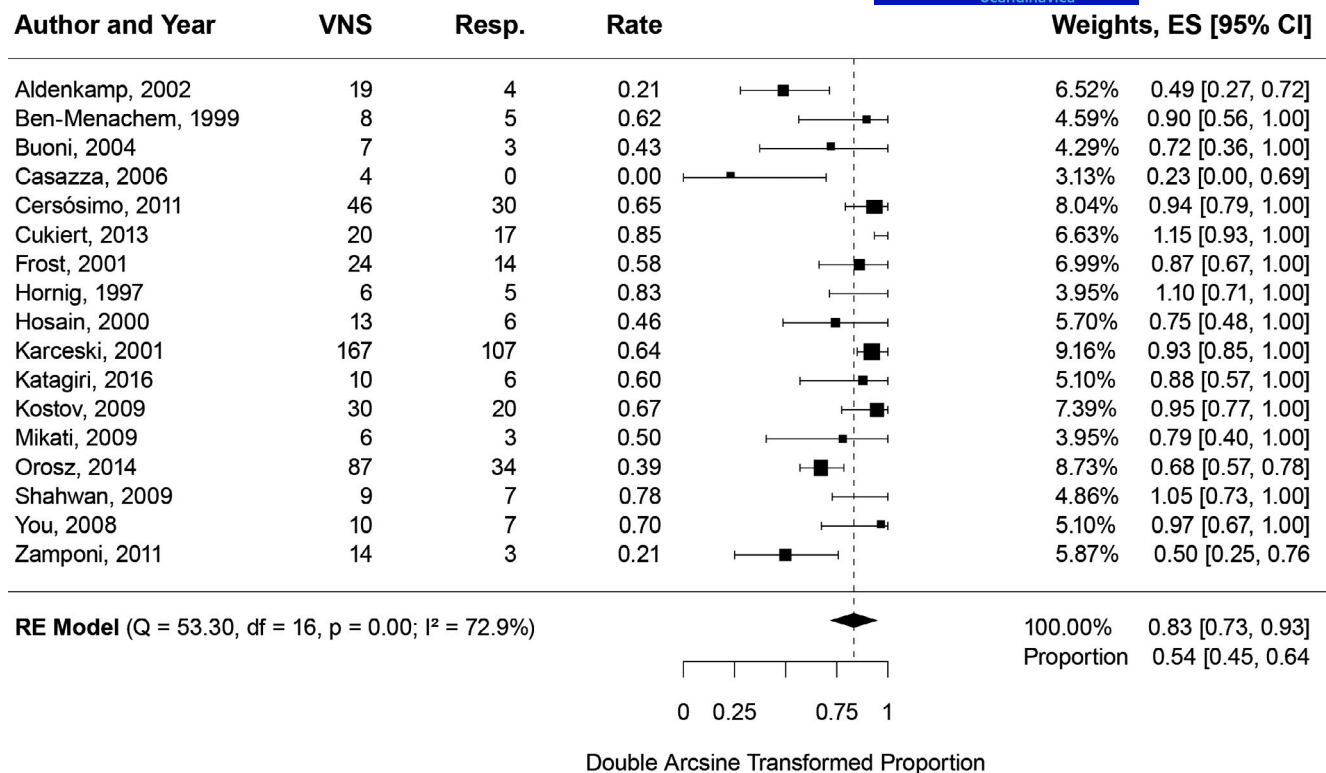
prospective design. Responder rate was not affected by study design:  $n = 10$ , proportion =  $0.56$  (95% CI:  $0.47$ ,  $0.66$ ) and  $n = 7$ , proportion =  $0.50$  (95% CI:  $0.28$ ,  $0.72$ ) for the retrospective and prospective studies, respectively (Figures S2 and S3).

### 3.4 | Appraisal of heterogeneity

Univariate meta-regression analyses were performed, based on Freeman-Tukey double arcsine transformation of study-specific proportions, to explore the relation between study-specific proportions and both year of publication and longest follow-up available.

There were no significant effects for year of publication ( $n = 17$ , slope coefficient =  $0.001$ ; 95% CI:  $-0.017$ ,  $0.020$ ;  $p$ -value =  $0.9$ ) (Figure S4) and length of study follow-up ( $n = 17$ , slope coefficient =  $-0.002$ ; 95% CI:  $-0.007$ ,  $0.003$ ;  $p$ -value =  $0.5$ ) (Figure S5).





**FIGURE 2** Forest plot displaying a random-effects meta-analysis (RE Model) of the primary endpoint. The 17 studies included in the analysis are listed in alphabetical order by the last author and publication year. The size of the square box is proportional to the weight that each study contributes to the meta-analysis, and the overall estimate is marked by a diamond. The primary endpoint was the proportion of responders (Resp.) among patients who received adjunctive VNS Therapy (VNS) who reported  $\geq 50\%$  reduction in seizure frequency (Response Rate=Resp./VNS) at the longest available follow-up period during treatment with adjunctive VNS Therapy. A total of 271 out of 480 patients responded to treatment. The pooled proportion (using the double arcsine back transformation) of responders produced weighted effects size (ES) estimates for each study. The mean estimated proportion demonstrates that 0.54 of patients with LGS responded with adjunctive VNS Therapy (95% CI: 0.45, 0.64; Cochran's Q = 53.3; degrees of freedom [df] =16; Qp-value for heterogeneity <0.001; I<sup>2</sup> = 72.9%)

### 3.5 | Exploratory safety analysis

The proportion of participants with serious adverse events and mild transient adverse events were analyzed based on means of a random-effects model. The pooled proportion (back transformation) of participants with serious adverse events was an estimate of 0.09 (95% CI: 0.05, 0.014) with 11 studies included (I<sup>2</sup> = 0%; Q p-value = 0.4), and the proportion of participants with mild transient adverse events was an estimate of 0.33 (95% CI: 0.15, 0.54) with six studies included (I<sup>2</sup> = 76.3%; Q p-value <0.001), respectively (Table S3).

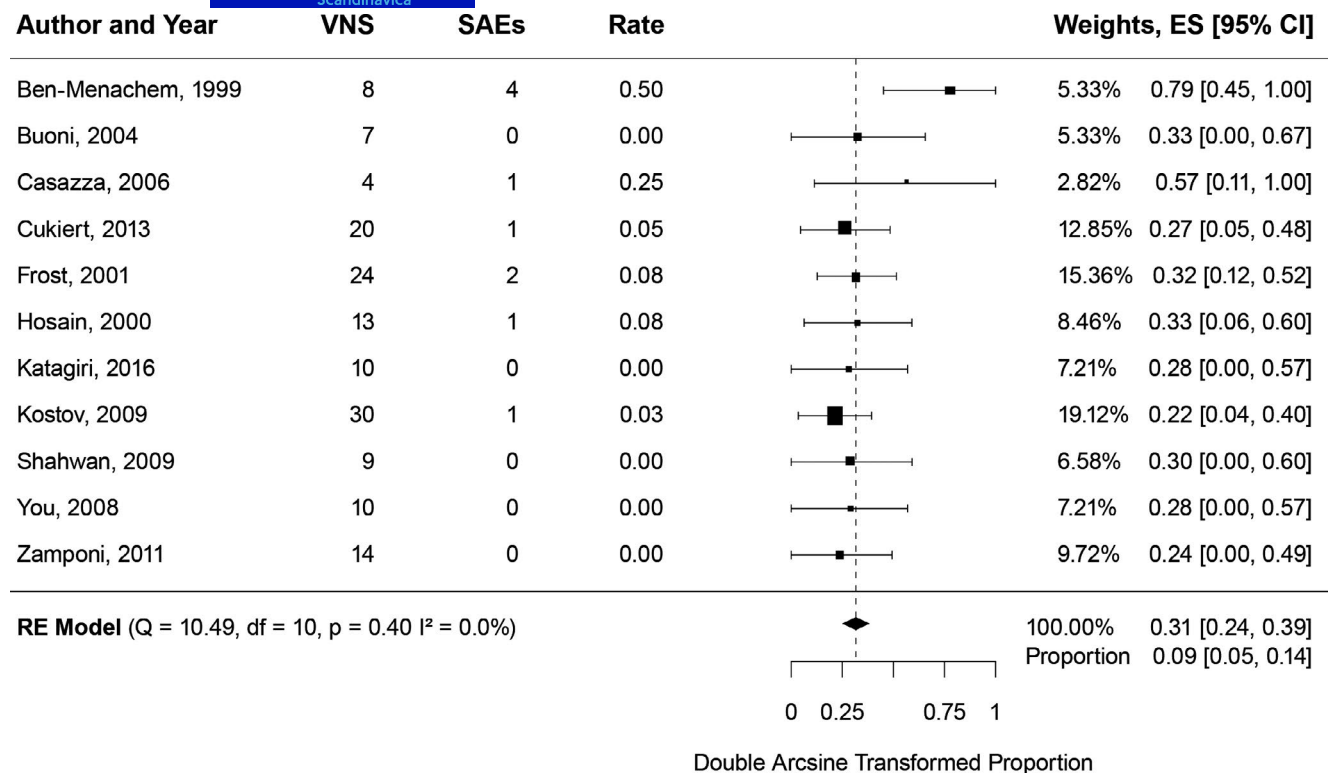
Figure 3 and Figure S6, respectively, report the forest plots of studies that reported serious adverse events (11 studies) and mild transient adverse events (6 studies).

Eight cases of death were reported in the included studies: one due to cancer, one due to pneumonia, three due to SUDEP and three due to status epilepticus. Two cases of SUDEP were not included in the serious adverse events analysis, as they did not occur in patients with LGS. The deaths due to pneumonia and cancer were also not included in the analysis due to these events not being considered potential adverse events of VNS Therapy. The remaining 4 deaths

(1 SUDEP and 3 status epilepticus)—all reported in one study—were included in the serious adverse analysis.

## 4 | DISCUSSION

This meta-analysis of 17 articles comprising 480 patients with LGS found 54% of patients to experience more than 50% seizure frequency reduction after treatment with vagus nerve stimulation. Furthermore, exploratory analysis of adverse events associated with VNS Therapy in patients with LGS calculated an incidence of serious adverse events of 9% from 11 studies, and an incidence of mild transient adverse events of 33% from 6 studies. Serious adverse events included 4 deaths: 1 due to SUDEP and 3 due to status epilepticus. An incidence rate for epilepsy-related mortality or SUDEP in patients with LGS could not be calculated in this analysis as patient years of VNS Therapy in LGS patients were not reported in the included studies. Mortality and SUDEP rates for all patients receiving VNS Therapy in the United States have been published by Ryvlin et al in 2017 who found all-cause mortality rates of 13.1 per 1000 patient years and SUDEP rates of rates of 2.47 and 1.68 per 1000 patient years of VNS



**FIGURE 3** Forest plot displaying a random-effects meta-analysis (RE Model) of serious adverse events (SAEs) reported for each study. The 11 studies with relevant data are listed in alphabetical order by the last author and publication year. The size of the square box is proportional to the weight that each study contributes to the meta-analysis and the overall estimate is marked by a diamond. The proportion of patients who experienced SAEs among patients who received adjunctive VNS Therapy (VNS) is presented (Rate = SAEs/VNS). A total of 10 out of 149 patients experienced serious adverse events and the pooled proportion (using the double arcsine back transformation) produced weighted effects size (ES) estimates and 95% confidence interval (CI) for each study. The mean estimated proportion demonstrates that 0.09 of patients with LGS experienced serious adverse events with adjunctive VNS Therapy (95% CI: 0.05, 0.14; Cochran's Q = 10.49; degrees of freedom [df] = 10; Qp-value for heterogeneity = 0.40; I<sup>2</sup> = 0.0%)

Therapy in years 1–2 and in years 3–10, respectively. All-cause mortality and SUDEP rates of VNS Therapy have yet to be reported for patients with LGS specifically; however, mortality and SUDEP rates in the full US VNS population reported in Ryvlin et al 2017 suggest that VNS Therapy is associated with similar mortality rates as reported for patients with drug-resistant epilepsy without VNS and that SUDEP rates may decline in the course of therapy.

The majority of the included studies are case series of 10–50 patients with different epilepsy etiologies in which patients with LGS represent the largest subgroup, possibly reflecting the frequent use of VNS Therapy in this patient population. In Orosz et al.'s retrospective multicenter analysis of 347 pediatric patients treated with VNS Therapy, which remains the largest analysis of VNS Therapy in children to date, LGS represented the largest subgroup in the study with 87 children. Orosz et al found a 39% responder rate for LGS patients at 24 months which was comparable to the 43.8% responder rate calculated for the full population at 24 months. The largest trial included in our analysis, Karceski et al 2001 found the noticeably higher responder rate of 64% in this cohort of adults and children with LGS treated with VNS Therapy. This analysis of all patients with LGS the VNS Patient Registry in the United States included 552 patients with LGS treated with VNS Therapy. However, responder rates were only reported for a fraction of these patients

and therefore only these 167 could be included in the present analysis. The study did however analyze patients with LGS who had previous callosotomy separately from those who did not, but found no striking difference in responder rate between the two groups at 12 months of follow-up (57% in patients with prior callosotomy vs. 65% without prior callosotomy). The third largest study included in the present analysis comprising 46 patients with LGS with a mean age of 13 years (range: 5–19.5 years) found a 65% responder rate. In this analysis, Cersosimo et al classify outcomes by McHugh classification offering greater granularity into the effects of VNS in LGS patients. The McHugh classification is adapted from the Engels classification for epilepsy surgery outcomes and is a specific classifier for seizure burden after VNS Therapy. Cersosimo et al report that 61% of LGS patients treated with VNS Therapy experienced a class 1A outcome meaning that they experienced 80%–100% seizure frequency reduction and a reduction in ictal or post-ictal severity.

#### 4.1 | Integration of VNS into a treatment algorithm for LGS

Patients with LGS experience several types of seizures including atypical absences, tonic postural seizures, tonic seizures, and



generalized tonic-clonic seizures; and a single treatment is not likely to be effective in treating such a seizure spectrum. Due to their complex seizure types and poor response to AEDs, patients with LGS are difficult to treat and often require polypharmacy of high doses of AEDs which is associated with a high side-effect burden. This may elicit or aggravate cognitive and behavioral problems which represents an additional burden for patients and caregivers.

Treatment is usually initiated with one or more antiepileptic drugs (AEDs) and progresses over time to a polypharmacy of AEDs. Adjunctive treatment with non-pharmacological options are considered when seizure control is not achieved with AEDs, and the non-pharmacological treatment options include ketogenic diet, resective surgery, corpus callosotomy, and VNS<sup>1,30</sup>

The ketogenic diet has been shown to be efficacious in the treatment of LGS with 47% to 51% of pediatric patients achieving >50% reduction in seizure frequency following 3–36 months of ketogenic diet therapy.<sup>1,31</sup> This adjunctive dietary therapy (and other related dietary therapies such as modified Atkins or low-glycemic index) can offer increased seizure control with a rapid onset effect, usually observed within 3 months. Effective therapy with the ketogenic diet requires compliant patients and dedicated caregivers and as such, long-term treatment adherence is one of the major issues with the ketogenic diet.<sup>1</sup>

Resective surgery is a treatment option in LGS patients with focal pathology and there is a high probability of seizure control in about 50% of patients following surgery.<sup>32</sup> Patients are carefully identified for resective surgery based on congruent findings of a definitive structural lesion using electroencephalogram (EEG), magnetic resonance imaging (MRI), and functional neuroimaging. Patients without identifiable localized brain lesion can be re-evaluated after treatment with VNS Therapy or corpus callosotomy, when generalized epileptiform discharges may become more localized. Generally, resective surgery is only indicated in focal pathology rendering it unsuitable for a majority of LGS patients.

Corpus callosotomy is considered in patients with LGS who are experiencing frequent debilitating drop seizures, which are mostly atonic in nature. Corpus callosotomy has been found to be more effective in reducing the frequency of atonic seizures in LGS patients compared with VNS Therapy; and in contrast, the same study found VNS Therapy to be more effective in reducing myoclonic seizures compared with corpus callosotomy.<sup>18</sup> Both corpus callosotomy and VNS Therapy appear to have similar effectiveness in reducing other seizure types in LGS patients; however, corpus callosotomy includes risks associated with craniotomy as well as a risk of disconnection syndrome.<sup>1,33</sup>

In the 2017 Expert Consensus on LGS treatment,<sup>1</sup> Cross et al highlighted the importance of patient-centered therapeutic approaches; for example, focusing on treating the most disabling seizure type (which may vary among patients and be highly dependent on their living situation) instead of seizure freedom. Cross et al also stressed that clinicians should focus on the overall quality of life when considering therapy for LGS and be vigilant about the negative impact of adverse drug effects on patients' quality of life.

Furthermore, the expert consensus recommended early integration of non-pharmacological treatments into LGS treatment strategies, including VNS Therapy.

VNS Therapy may be a valuable option that might increase seizure control in LGS patients together with a reduction of medication burden (as evidenced in patients with drug-resistant epilepsy<sup>34</sup>) and improvement of the cognitive and behavioral consequences associated with multiple AEDs administration.

Results from our meta-analysis suggests that adjunctive VNS Therapy is effective in reducing seizure burden in patients with LGS and the seizure reduction is comparable to that observed in heterogeneous drug-resistant epilepsy populations.<sup>35</sup> Therefore, it is relevant to consider the optimal positioning of VNS Therapy within a treatment algorithm for LGS and patients with LGS should be carefully evaluated for VNS Therapy implantation before more invasive palliative surgical procedures.

## 4.2 | Exploratory analysis of safety findings

The incidence of serious adverse events associated with VNS in patients with LGS in this analysis (9%; 95% CI: 5%, 14%) was higher than reported in long-term efficacy studies of heterogeneous cohorts with drug-resistant epilepsy (1.4%–2.4%).<sup>36,37</sup> This may potentially be attributed to variances in definition of serious and mild transient adverse events across the included studies. For example, due to incomplete reporting on treatment of infection in some of the included studies, any infection had to be considered a serious adverse event in this analysis, irrespective of whether it could be treated conservatively or required device removal, whereas other trials consider infection not requiring device removal a mild adverse event.

## 4.3 | Clinical and surgical considerations related to VNS therapy device implantation in patients with LGS

Here a clinical and surgical overview to facilitate understanding of the use of VNS Therapy in the treatment of patients with LGS is provided.

Similar to neurosurgical shunt surgeries, implanting a VNS Therapy pulse generator and silicone leads benefits from a standardized reproducible approach that ensures a quick procedure, minimizes errors, and has a low infection risk. As the surgery involves implanting a *corpus alienum*, there is generally a greater than average risk of infection; however, based on analysis of VNS implantation surgeries performed between 2005 and 2016, the procedure has a post-operative infection risk of 1.3% which is within the normal range per the guidelines from the American College of Surgeons and Surgical Infection Society.<sup>38–40</sup>

VNS device implantation is performed under general anesthesia with the patient in supine position with the head slightly extended. After sterile prep and drape, a skin crease neck incision is placed. Platysma is divided, followed by subplatysmal dissection in cranial and caudal direction. The cervical section of the vagus nerve runs

within the carotid sheath in a parallel course along the carotid artery. However, the position varies between patients and in a minority of patients, the vagus nerve is localized dorsomedially between the carotid artery and internal jugular vein as stated in textbooks.<sup>41,42</sup> Ultrasound is an easy and non-invasive method of localizing the vagus nerve prior to and during surgery; the carotid is a round pulsating non-compressible structure, the jugular vein is lateral to this and is more oval shaped and easily compressible. Similar to other nerves, the vagus nerve appears dark on ultrasound and its course continues to be parallel to the carotid.

Implanting a VNS Therapy device consists of three steps: placement of the electrode contacts around the vagus nerve, tunneling of the leads, and placement of the pulse generator. The order in which this is done varies between surgeons; however, it is advisable to perform the steps in the listed standardized order.<sup>43</sup>

In order to obtain a clear interface between contacts and the vagus nerve for optimal VNS Therapy response, the vagus nerve needs to be well dissected from its surrounding tissues without compromising the nerve or the surrounding vasculature and exiting branches.

The pocket for the implantable pulse generator (IPG) is created in the left pectoral region. Subcutaneous placement of the generator right on top of the musculus pectoralis fascia instead of a sub-fascial placement is practical and less invasive and ensures optimal communication between the IPG and the VNS Therapy programming system. However in some patients, auto-manipulation of the wound or tampering with the IPG after wound healing ("twiddling") may be a concern.<sup>44</sup> This may be specifically relevant in patients with LGS in the case of significant cognitive impairment, autistic traits, and behavioral problems. Sub-fascial placement may then be beneficial as the deep localization makes it less prone to displacement and infection. Interscapular placement may be considered<sup>45</sup>; however, it is important to note that this will likely impair the use of the cardiac-based seizure detection feature of responsive VNS Therapy generators, as these devices rely on continuous monitoring of the electrocardiogram (ECG) measured as the vector between the electrodes and the IPG positioned in a pectoral location. Interscapular placement of the IPG will alter QRS morphology which may prevent correct detection by the cardiac-based seizure detection algorithm. Hence, before interscapular placement, it should be considered whether the patient is significantly impaired by a seizure type associated with ictal tachycardia, which may potentially be aborted or reduced in intensity by responsive VNS Therapy. Furthermore, in order to prevent migration of the generator it should be anchored to the fascia, which again may be of extra importance in patients with LGS.

As with all neurostimulation devices, after connecting the IPG to the electrodes and before wound closure, acceptable impedance should be confirmed. Additionally, in responsive VNS Therapy devices, correct sensing of the ECG should be confirmed, as incorrect sensing may require repositioning of the IPG.

Absolute hemostasis is secured and both wounds are closed in layers. Wound drains are not typically placed in this procedure. Incision sites are dressed with waterproof dressing and patients are commonly discharged on the same day of surgery or the next day.<sup>38</sup>

Malfunction due to (partial) lead break is a known possible long-term complication in VNS, especially with the older model of more flexible leads. In patients with LGS, such a malfunction can easily lead to status epilepticus with devastating effects.<sup>46</sup> Therefore, if indicated the patient should be swiftly advanced to revision surgery in which assuring the integrity of the vagus nerve is always the primary goal. If needed, the fractured electrode can be cut below the helices and left in place and the new electrodes placed along an adjacent section of the vagus nerve. In general, a complete removal can be safely achieved in which the use of microsurgical techniques and the microscope are highly recommended.<sup>47,48</sup>

#### 4.4 | Strengths and limitations

This report represents the most comprehensive meta-analysis of VNS Therapy in LGS patients and has prospectively analyzed potential sources of bias that often negatively impact analyses of this nature. However, the results reported here is limited by the inherent property of meta-analyses of ignoring potentially important differences across studies as well as by the low patient-level insight in the identified studies. Furthermore, some of the included studies have small sample sizes and only meet American Academy of Neurology Class III evidence criteria for therapeutic studies.

### 5 | CONCLUSIONS

LGS is a severely drug-resistant epileptic syndrome. As patients with LGS who receive adequate treatment very early in their disease process have been documented to have a more favorable overall outcome, the early integration of VNS Therapy should be considered as it may improve the negative consequences of both seizures and epileptic abnormalities. This meta-analysis suggests that VNS is a well-tolerated and effective adjunctive treatment for patients with LGS resulting in a responder proportion of 54% (95% CI: 45%, 64%), which is comparable to response in heterogeneous drug-resistant epilepsy populations. VNS Therapy may be a valuable treatment to increase seizure control in patients with LGS, and patients with LGS should be carefully evaluated for VNS Therapy implantation before more invasive palliative surgical procedures.

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#### CONFLICT OF INTEREST

MD and TG are employees of LivaNova, the manufacturer of VNS Therapy System and MD holds stock options. NS has received support from LivaNova and has served as a paid consultant for LivaNova.

JS has received a research grant from LivaNova. ZT, DH, HJS, and MAK declare that they have no conflict of interest.

## COMPLIANCE WITH ETHICAL STANDARDS

Ethics approval and informed consent are not applicable as the manuscript contains clinical data that has been previously published.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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