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LITERATURE REVIEW

The role of vagus nerve stimulation in genetic etiologies of drug-resistant epilepsy: a meta-analysis

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OBJECTIVE Drug-resistant epilepsy (DRE) affects many children. Vagus nerve stimulation (VNS) may improve seizure control; however, its role in children with genetic etiologies of epilepsy is not well described. The authors systematically reviewed the literature to examine the effectiveness of VNS in this cohort.

METHODS In January 2021, the authors performed a systematic review of the PubMed/MEDLINE, SCOPUS/Embase, Cochrane, and Web of Science databases to investigate the impact of VNS on seizure outcomes in children with genetic etiologies of epilepsy. Primary outcomes included seizure freedom rate, ≥ 90% seizure reduction rate, and ≥ 50% seizure reduction rate. Secondary outcomes were seizure severity and quality of life (QOL), including cognitive, functional, and behavioral outcomes. A random-effects meta-analysis was performed.

RESULTS The authors identified 125 articles, of which 47 with 216 nonduplicate patients were analyzed. Common diagnoses were Dravet syndrome (DS) (92/216 patients [42.6%]) and tuberous sclerosis complex (TSC) (63/216 [29.2%]). Seizure freedom was not reported in any patient with DS; the pooled proportion (95% CI) of patients with ≥ 50% seizure reduction was 41% (21%–58%). Secondary cognitive outcomes of VNS were variable in DS patients, but these patients demonstrated benefits in seizure duration and status epilepticus. In TSC patients, the pooled (95% CI) seizure freedom rate was 40% (12%–71%), ≥ 90% seizure reduction rate was 31% (8%–56%), and ≥ 50% reduction rate was 68% (48%–91%). Regarding the secondary outcomes of VNS in TSC patients, several studies reported decreased seizure severity and improved QOL outcomes. There was limited evidence regarding the use of VNS to treat patients with other genetic etiologies of epilepsy, such as mitochondrial disease, Rett syndrome, Doose syndrome, Landau-Kleffner syndrome, Aicardi syndrome, Angelman syndrome, ring chromosome 20 syndrome, and lissencephaly; variable responses were reported in a limited number of cases.

CONCLUSIONS The authors conducted a systematic review of VNS outcomes in children with genetic etiologies of DRE. Among the most studied conditions, patients with TSC had substantial seizure reduction and improvements in QOL, whereas those with DS had less robust seizure reduction. Increased testing, diagnosis, and long-term follow-up studies are necessary to better characterize VNS response in these children.

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KEYWORDS drug-resistant epilepsy; surgical epilepsy; vagus nerve stimulation; genetic epilepsy; pediatric

Drug-resistant epilepsy (DRE) affects an estimated 30%–40% of patients with epilepsy,[1,2] resulting in worse mortality, cognitive impairment, and quality-of-life (QOL) outcomes.[3] In children, epilepsy may occur for a variety of reasons; however, genetic etiologies are increasingly recognized. Underlying genetic causes of epilepsy include single gene mutations related to channelopathies, disordered synaptic transmission, chromosomal abnormalities, and microdeletions, among others.[4] Examples include Dravet syndrome (DS), with mutations in *SCN1A* altering neuronal voltage-gated sodium ion channels;[5,6] Doose syndrome, with multiple genetic mutations affecting genes such as *SCN1A*, *SCN1B*, and *GABRG2*;[7] and Rett syndrome, with *MECP2* gene mutations on chromosome Xq28.[8] Mitochondrial diseases can result in underlying genetic-metabolic etiologies of epilepsy.[9] Addi-

ABBREVIATIONS DRE = drug-resistant epilepsy; DS = Dravet syndrome; QOL = quality of life; TSC = tuberous sclerosis complex; VNS = vagus nerve stimulation.

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tionally, structural genetic abnormalities such as tuberous sclerosis complex (TSC) cause epilepsy.[10] Although these are among the more commonly regarded genetic etiologies of epilepsy, many genetic mutations exist and contribute to epilepsy, and many more are of unknown clinical or pathological significance.

Seizure control is paramount in pediatric epilepsy. Children with DRE benefit from early intervention to reduce seizures and minimize neurodevelopmental delays.[11,12] In the literature, 20%–40% of patients with DRE are described as candidates for epilepsy surgery.[12] In 1997, vagus nerve stimulation (VNS) was approved by the US Food and Drug Administration as an adjunctive therapy for patients > 12 years of age with DRE and partial-onset seizures.[13] In 2017, the Food and Drug Administration extended this approval to include younger children > 4 years of age with DRE and partial-onset seizures.[14] Since then, VNS has been considered a well-tolerated treatment with a reasonable adverse effect profile for patients with DRE who are poor candidates for epilepsy surgery or have undergone failed epilepsy surgery.[12,13] In cohorts of children with DRE of any etiology, 37.6%–64.8% of patients were responders and achieved at least 50% seizure reduction with VNS treatment.[15–17]

Despite multiple tools in the treatment armamentarium for pediatric epilepsy, antiepileptic drugs, dietary modifications, and epilepsy surgery fail to achieve adequate seizure control in some patients with DRE. The role and timing of all treatment modalities, including VNS, continue to be explored and characterized for this challenging disease.[3] Although the impact of VNS has been examined systematically in adults and children with all etiologies of epilepsy,[18] as well as in large cohorts of children with various etiologies of DRE,[15,17] its role in genetic etiologies of epilepsy has not been specifically characterized in children. We aimed to systematically review the literature and to use a meta-analysis to examine the effectiveness of VNS in pediatric patients with a genetic etiology of DRE. Our objectives were to 1) determine the most studied genetic etiologies of DRE treated with VNS, 2) identify which types of etiology have the best outcomes associated with VNS, and 3) identify which types may be best served with future study.

Methods

A systematic review was conducted to investigate the impact of VNS on seizure outcomes in pediatric patients with genetic etiologies of epilepsy. The search protocol, which included the research question and inclusion and exclusion criteria, was developed in accordance with the PRISMA guidelines. Our expert in medical library sciences was consulted to design and implement this structured search (see *Acknowledgments*).

Search Strategy

We performed a comprehensive search in January 2021 of the following databases: PubMed/MEDLINE, SCOPUS/Embase, Cochrane, and Web of Science. There were no date restrictions. Concept categories were searched, and the results were combined using appropriate Boolean operators. Categories included pediatric patients with genetic etiology of DRE, VNS treatment, and outcomes. Related terms were also incorporated into the search strategy to ensure that all relevant articles were retrieved (Supplemental Data). Additional relevant articles were added by manually searching the references of the retrieved review articles.

Selection Criteria

Duplicate articles and those not written in the English language were removed. The remaining articles were screened for full-text review on the basis of the relevance of the title and abstract. We reviewed the full text of each article, and the final articles were selected on the basis of a systematic assessment of the inclusion and exclusion criteria. We included studies that 1) included patients with a specified or presumptive genetic etiology of DRE, 2) evaluated treatment with VNS, and 3) included at least 1 pediatric patient ≤ 18 years of age. We excluded 1) studies that could not differentiate pediatric from nonpediatric patients, 2) review articles, and 3) studies that lacked sufficient outcome data regarding the impact of VNS on seizure control and/or QOL.

Data Collection and Analysis

Primary outcomes included seizure freedom rate, ≥ 90% seizure reduction rate, and ≥ 50% seizure reduction rate, which was also defined as the responder rate.[13,16,19,20] These outcomes were reported for large cohorts[15–17] or extrapolated from smaller studies that reported Engel or McHugh classifications.[21–23] The ≥ 50% seizure reduction rate, ≥ 90% seizure reduction rate, and seizure freedom rate were calculated by pooling the individual participant responses, when available and reported, pertaining to each genetic etiology of epilepsy identified in each study. Secondary outcomes were seizure severity and QOL outcomes, including cognitive, functional, and behavioral outcomes. The following data were extracted from the selected articles: bibliographic data, study design, total number of patients, specific number of pediatric patients who met our criteria, genetic etiology of epilepsy, and seizure outcomes after VNS implantation. Full-text articles and extracted data were reviewed by one author (S.H.) and then verified by a second author (M.A.L.).

Statistical Analysis

Random-effects meta-analysis was performed in this study. Because the proportions were equal to 0 or 1 in some studies, Freeman-Tukey double arcsine transformation was applied. The I^2 statistic was used to estimate heterogeneity, and Egger's test was used to estimate publication bias. Pooled proportions and exact binomial confidence intervals were reported. A p value < 0.05 was considered significant. Analysis was done by using Stata version 16.1 (StataCorp).

Quality Assessment

Quality of evidence was evaluated on the basis of the study design grades by Shadish et al.[24]

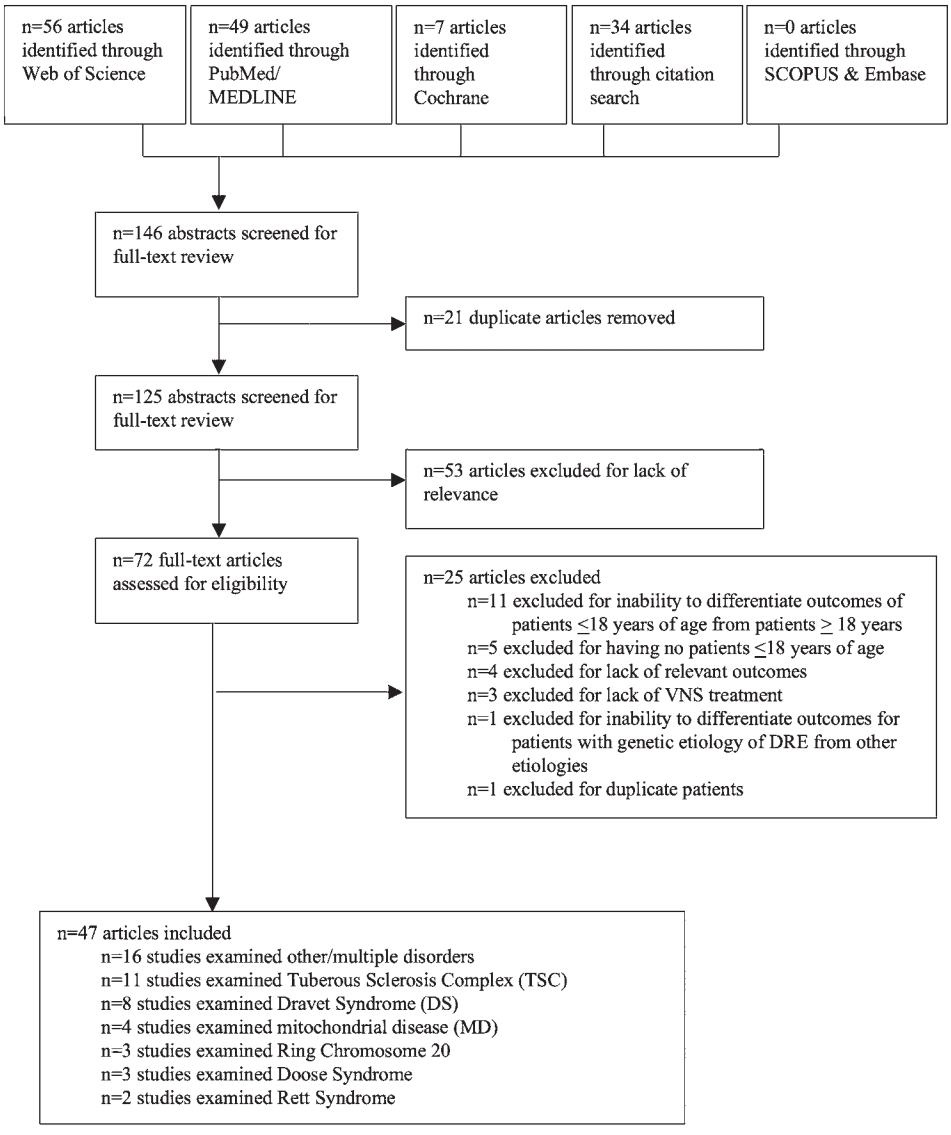

FIG. 1. This PRISMA flowchart demonstrates our search strategy for 4 databases. Duplicate articles were excluded, as well as those that lacked relevance or did not meet the established inclusion criteria related to patient, intervention, or outcome characteristics.

Results

Search Results

The search strategy is summarized in the PRISMA flowchart (Fig. 1). The initial search yielded 125 articles. Screening these articles by abstract, followed by full-text review, yielded a total of 47 articles included.

Study Characteristics

Of the 47 articles, none were clinical trials. The articles included retrospective cohort studies (n = 29), prospective cohort studies (n = 9), and case reports (n = 9).

Patient Characteristics

We analyzed 216 nonduplicate patients from 47 articles. The majority of studies reported a larger cohort of patients than from whom we extracted data, because only pediatric patients were examined in this study. This was the case for all but 4 retrospective studies, in which the total number of patients was equal to the number of patients included in our review.[8,9,25,26] The most common diagnoses were DS (92/216 patients [42.6%]) and TSC (63/216 [29.2%]). The types of genetic etiologies of DRE, numbers of patients with each diagnosis, and numbers of referenced studies are depicted in Table 1.

Impact of Genetic Etiology on DRE Has Been Most Studied in Patients With DS and TSC

Fifteen articles with 92 total patients studied DS. Seizure freedom was not reported by any patient. Two studies reported the proportions of patients with ≥ 90% seizure reduction, which were 100% (1/1 patient) and 50% (1/2 pa-

TABLE 1. Studied genetic etiologies of DRE

Genetic Etiology of DRE	No. (%) of Patients	No. of Referenced Studies
DS	92 (42.6)	15[6,14,23–35]
TSC	63 (29.2)	18[15,20–22,32,35–47]
MD	11 (5.1)	6[9,36,40,48–50]
Rett syndrome	11 (5.1)	5[8,33,36,47,51]
Doose syndrome	10 (4.6)	6[28,31,34,52–54]
Landau-Kleffner syndrome	7 (3.2)	2[37,68]
Aicardi syndrome	6 (2.8)	2[37,69]
Angelman syndrome	5 (2.3)	3[38,55,70]
r(20)	3 (1.4)	3[71–73]
Lissencephaly	3 (1.4)	2[35,37]
Other etiologies*	5 (2.3)	4[34,37,55,74]

MD = mitochondrial disease; r(20) = ring chromosome 20 syndrome.
* Included Mosaic Turner syndrome, Coffin-Siris syndrome, *CDKL5* mutation, subcortical band heterotopia, and Down syndrome.

tients), respectively.[27,28] Thirteen articles were used to calculate the pooled proportion of patients with ≥ 50% seizure reduction.[6,15,25–35] The pooled proportion (95% CI) was 41% (21%–58%) (36/88 patients) (Fig. 2). VNS had a significant effect on the proportion of patients with ≥ 50% seizure reduction ($Z = 5.75$, $p < 0.001$). Heterogeneity ($I^2 = 40.96\%$, $p = 0.06$) and publication bias ($p = 0.772$) were nonsignificant.

Regarding the secondary outcomes of VNS in patients with DS, Fulton et al. saw improved cognition and speech in 44.9% (4/9 patients)[25] and Zamponi et al. found that all 7 DS patients had unchanged cognitive levels after 1 year.[6] Shahwan et al. reported briefer seizures in a responder[35] and Sirsi et al. reported briefer seizures in a nonresponder,[26] indicating that the benefit of VNS may exist even if seizure reduction is limited. Sirsi et al. also reported decreased episodes of status epilepticus in the same nonresponder who had briefer seizures, which greatly improved QOL.[26] Furthermore, Sirsi et al. examined a breakdown of response according to *SCN1A* gene alterations, including 1 patient with a known disease-associated

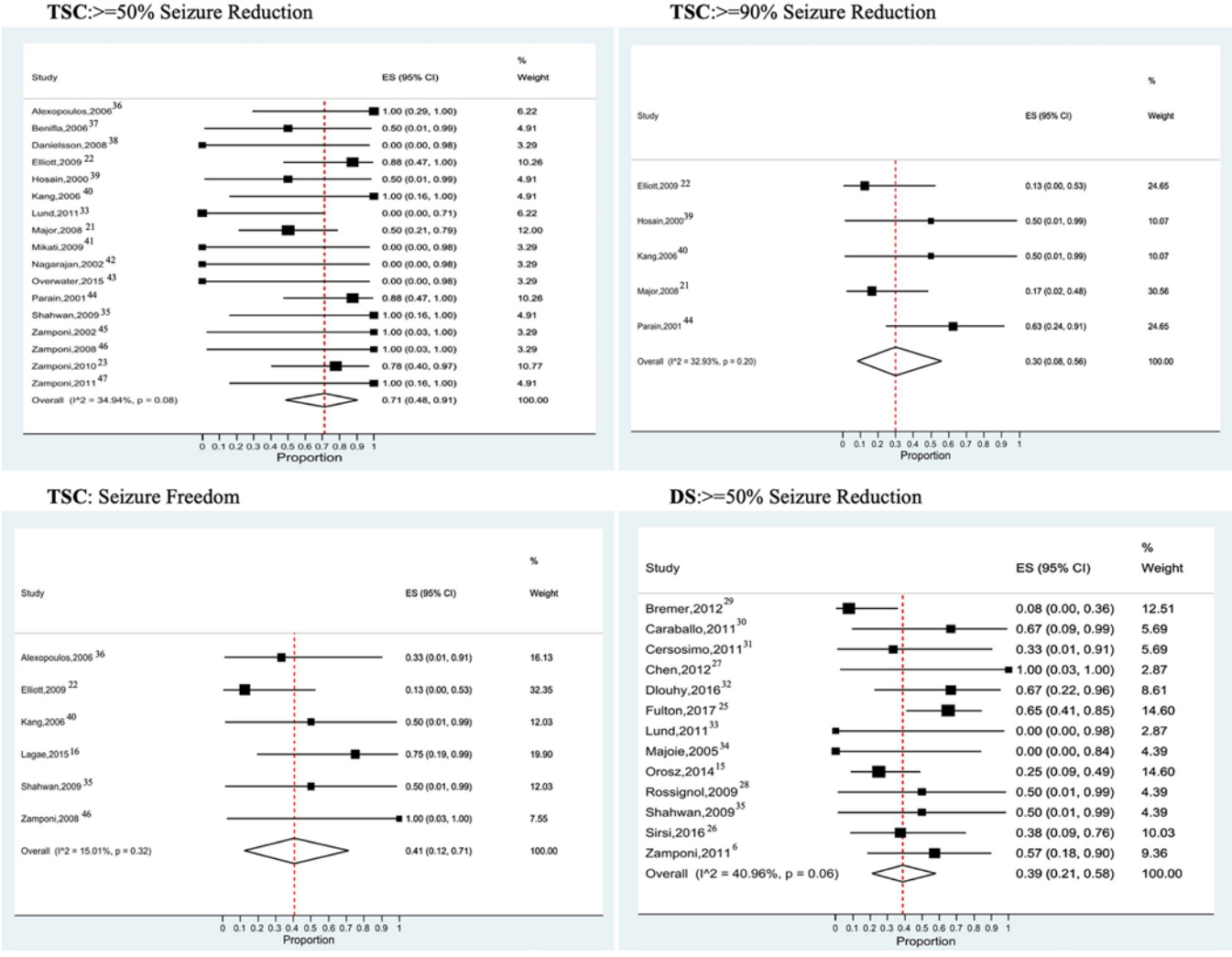

FIG. 2. Statistical analysis of seizure outcomes in patients with TSC and DS. In this study, effect size (ES) was the proportion of patients with seizure reduction. This figure depicts the ES values of studies that included patients with TSC and DS who had seizure freedom, ≥ 90% seizure reduction, and ≥ 50% seizure reduction. Figure is available in color online only.

mutation, 1 with a predicted disease-associated mutation, 1 with a disease-causing whole-gene deletion, and 4 with unclear genetic variants;[26] the patient with whole-gene deletion had the best response to VNS treatment (> 75% seizure reduction).

Eighteen articles with 63 total patients studied TSC (Table 2).[16,21–23,33,35–47] Of these, 55 patients in 14 articles had not previously undergone epilepsy surgery.[16,21–23,36,38–42,44–47] In the other articles,[33,35,37,43] it was unclear if the included patients underwent prior surgery. The results of the random-effects meta-analysis showed that VNS had a significant effect on the seizure freedom rate ($Z = 3.62$, $p < 0.001$), ≥ 90% seizure reduction rate ($Z = 3.48$, $p < 0.001$), and ≥ 50% seizure reduction rate ($Z = 7.50$, $p < 0.001$) (Fig. 2). The pooled (95% CI) seizure freedom rate was 40% (12%–71%) (8/20 patients), the pooled ≥ 90% seizure reduction rate was 31% (8%–56%) (10/32 patients), and the pooled ≥ 50% seizure reduction rate was 68% (48%–91%) (40/59 patients). No significant heterogeneity and publication bias was found in the analyses of seizure freedom rate ($I^2 = 15.01\%$ and $p = 0.32$ for heterogeneity; $p = 0.092$ for bias), ≥ 90% seizure reduction rate ($I^2 = 32.93\%$ and $p = 0.20$ for heterogeneity; $p = 0.448$ for bias), and ≥ 50% seizure reduction rate ($I^2 = 34.94\%$ and $p = 0.08$ for heterogeneity; $p = 0.317$ for bias).

Regarding the secondary outcomes of patients with TSC, several studies reported decreased seizure severity[21–23,41,42,44] and improved functional, behavioral, and cognitive outcomes.[21–23,38,44,46] Major and Thiele found no significant association between type of TSC mutation (*TSC1* or *TSC2*) and outcome of VNS.[21] Lagae et al. found a significant association between seizure freedom and VNS implantation at a younger age.[16] Sustained efficacy was more likely in children who underwent implantation before 5 years of age and children with shorter epilepsy duration prior to VNS.[16] Alexopoulos et al. also found this association in patients under 12 years of age.[36] Zamponi et al. observed the greatest benefit in adaptive behaviors, particularly communication, and increased cognitive level in children who underwent implantation before 6 years of age.[23]

Limited Evidence of Effectiveness of VNS in Patients With Other Specific Genetic Etiologies of Epilepsy

Six articles with 11 total patients studied mitochondrial disease,[9,36,40,48–50] of whom 8 (72.7%) were nonresponders.[9,36,40] Five articles with 11 total patients studied Rett syndrome.[8,33,36,47,51] The ≥ 50% seizure reduction rate was 81.8% (9/11 patients).[8,33,36,47]

Six articles with 10 total patients studied Doose syndrome.[28,31,34,52–54] Among 9 patients with individual outcomes, 77.8% (7/9 patients) were responders.[28,31,34,53,54] Kanai et al. reportedly used VNS to completely resolve residual myoclonic seizures that remained after corpus callosotomy in a patient with Doose syndrome.[52] This principle was also seen in a patient with Down syndrome who had worthwhile seizure reduction (Engel class IIIA) due to VNS implantation after nonfocal seizures persisted despite corpus callosotomy.[55] Table 2 summarizes the evidence supporting VNS for these and other studied genetic etiologies. Data extracted from all included articles are detailed in Table 3.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to examine the effectiveness of VNS specifically in pediatric patients with genetic etiologies of DRE. We analyzed 216 patients across 47 articles. We found that VNS provides favorable outcomes in patients with TSC and good outcomes in those with DS. VNS for other etiologies of genetic DRE was not studied and reported enough to understand the responses of these patients.

The Role of VNS in Some Genetic Etiologies Is More Understood Than Others

In our review, the pooled ≥ 50% seizure reduction rate was 68% among TSC patients. In contrast, ≥ 50% seizure reduction rates reportedly range from 37.6% to 64.8% in children with DRE of any etiology,[15–17] and another pooled analysis of 481 children with all etiologies found a rate of 55%.[13] These findings suggest that children with TSC may respond favorably to VNS therapy, which is significant when considering alternatives to conventional resective surgery.[44] Patients with single dominant epileptogenic tubers may make excellent candidates for cranial surgery.[56] The majority, however, have multiple tubers and seizure foci that may not be addressed with 1 selective resective surgery.[22,56] These patients with diffuse disease or multifocal seizure onset may be poor candidates for conventional surgery[22,44] or have failed response to surgery, thereby making VNS a viable adjunctive treatment.[13] The VNS outcomes of children with TSC should be interpreted with caution. Our analysis, which was limited to the available studies, did not compare response to VNS of those patients who underwent failed resective surgery with those who were not considered candidates for intracranial surgery. The decision to pursue VNS treatment before or after resective surgery, if any, should be made on an individual patient basis.

In line with our findings, a meta-analysis found that TSC patients achieved significantly better outcome with VNS than those with unknown or idiopathic etiologies.[18] Posttraumatic epilepsy was the only etiology other than idiopathic epilepsy that predicted a significantly better response.[18] These patients are often poor surgical candidates because the epileptic foci cannot be localized,[57] similar to the challenge in TSC patients with multiple tubers. One suggested mechanism of VNS action in posttraumatic patients is to spare GABAergic neurons from loss, which may contribute to seizure reduction by maintaining an inhibitory tone.[58] Because cortical tubers can cause significant neuronal loss in gray matter,[59] this mechanism may also explain the protective effect of VNS in TSC patients.

In contrast to the high response rate of TSC patients, the pooled ≥ 50% seizure reduction rate was 41% among DS patients, and none were seizure free. Alternatively, seizure reduction was quite variable for the patients with other genetic etiologies of DRE included in our review, with few patients studied overall. Although the data were limited by small sample size, and therefore not statistically significant, our findings suggested that some etiologies of genetic epilepsy, such as mitochondrial disorders, may not have as favorable a benefit from VNS, whereas others, such as Rett and Doose syndromes, may have a favorable

TABLE 2. Outcomes of VNS treatment in pediatric patients with genetic etiologies of DRE

Study Characteristics			Primary Outcomes (no. [%])			Secondary Outcomes	
Authors & Year	Study Type	No. of Pediatric Patients	≥50% Seizure Reduction Rate	Seizure Freedom Rate	≥90% Seizure Reduction Rate	Cognitive, Functional, & Behavioral Improvements	Seizure Severity
DS							
Bremer et al., 2012[29]	R	13	1/13 (7.7)				
Caraballo, 2011[30]	R	3	2/3 (66.7)				
Cersósimo et al., 2011[31]	R	3	1/3 (33.33)			Improved mental age in responder	Decreased in responder
Chen et al., 2012[27]	R	1	1/1 (100)		1/1 (100)		
Dlouhy et al., 2016[32]	R	6	4/6 (66.7)				
Fernandez et al., 2015[75]*	R	3	Unspecified seizure reduction				Resolution of SE in 100% (3/3 patients) w/in 1 yr
Fulton et al., 2017[25]	R	20	13/20 (65)†			Improved cognition & speech	
Kokoszka et al., 2017[55]	R	1	Engel class IIIA (worthwhile seizure reduction)				
Lund et al., 2011[33]	R	1	0/1 (01)				
Majoie et al., 2005[34]	P	2	0/2 (0)				
Orosz et al., 2014[15]	R	20	5/20 (25)*				
Rossignol et al., 2009[28]	P	2	1/2 (50)		1/2 (50)		
Shahwan et al., 2009[35]	R	2	1/2 (50)			Shorter seizure duration in responder	Resolution of SE in responder
Sirsi et al., 2016[26]	R	8	3/8 (37.5)			Shorter seizure duration in a nonresponder	Decreased SE episodes in a nonresponder
Zamponi et al., 2011[6]	R	7	4/7 (57.1)			Slightly improved alertness & communication skills (7/7 patients [100%]) & significantly improved communication (1/7 [14.3%])	
TSC							
Alexopoulos et al., 2006[36]	R	3	3/3 (100)	1/3 (33.3)			
Benifla et al., 2006[37]	R	2	1/2 (50)				
Danielsson et al., 2008[38]	P	1	0/1 (0)			Improved social interactions & attention span	
Elliott et al., 2009[22]	R	8	7/8 (87.5)	1/8 (12.5)	1/8 (12.5)	Improved development & behavior	Decreased in 57% (4/7) of responders
Hosain et al., 2000[39]	P	2	1/2 (50)		1/2 (50)		
Kang et al., 2006[40]	P	2	2/2 (100)	1/2 (50)	1/2 (50)		
Lagae et al., 2015[16]	P	4		3/4 (75)			
Lund et al., 2011[33]	R	3	0/3 (0)				
Major & Thiele, 2008[21]	R	12	6/12 (50)		2/12 (16.7)	Improved alertness, development, & behavior	Decreased in 100% (6/6) of responders
Mikati et al., 2009[41]	R	1	0/1 (0)				Decreased
Nagarajan et al., 2002[42]	R	1	0/1 (0)				Decreased
Overwater et al., 2015[43]	R	1	0/1 (0)				
Parain et al., 2001[44]	R	8	7/8 (87.5)		5/8 (62.5)	Shorter seizure duration & improved alertness	Decreased
Shahwan et al., 2009[35]	R	2	2/2 (100)	1/2 (50)			
Zamponi et al., 2002[45]	P	1	1/1 (100)				
Zamponi et al., 2008[46]	R	1	1/1 (100)	1/1 (100)		Improved alertness & social interaction	

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Study Characteristics			Primary Outcomes (no. [%])			Secondary Outcomes	
Authors & Year	Study Type	No. of Pediatric Patients	≥50% Seizure Reduction Rate	Seizure Freedom Rate	≥90% Seizure Reduction Rate	Cognitive, Functional, & Behavioral Improvements	Seizure Severity
TSC (*continued*)							
Zamponi et al., 2010[23]	R	9	7/9 (77.8)			Reduction of aggressive behaviors; improved communication & cognitive level	Decreased in 57% (4/7) of responders; decreased intensity of drop attacks in 75% (3/4)
Zamponi et al., 2011[47]	R	2	2/2 (100)				
MD							
Alexopoulos et al., 2006[36]	R	2	0/2 (0)				
Arthur et al., 2007[9]	R	5	0/5 (0)				
Blount et al., 2006[49]	R	1	Seizure reduction (from multiple GTC seizures to 1 per night)			Shorter seizure duration & less intense seizures	
Fujimoto et al., 2012[48]	C	1	1/1 (100)	1/1 (100)		No improvement in cognitive level, myoclonus, or cerebellar symptoms (MERRF patient)	
Kang et al., 2006[40]	P	1	0/1 (0)				
Nolan et al., 2019[50]	C	1	Unspecified seizure reduction				
Rett syndrome							
Alexopoulos et al., 2006[36]	R	1	1/1 (100)				
Hornig et al., 1997[51]	P	1	0/1 (0)				
Lund et al., 2011[33]	R	1	1/1 (100)				
Wilfong & Schultz, 2006[8]	R	7	6/7 (85.7)		4/7 (57.1)	Improved alertness	
Zamponi et al., 2011[47]	R	1	1/1 (100)				
Doose syndrome							
Cersósimo et al., 2011[31]	R	3	2/3 (66.7)			Improved mental age in responders	Decreased in 100% (3/3 patients)
Majoie et al., 2005[34]	P	2	2/2 (100)		1/2 (50)		
Parker et al., 1999[54]	P	2	1/2 (50)				
Rossignol et al., 2009[28]	P	1	1/1 (100)	1/1 (100)			
Fan et al., 2014[53]	C	1	1/1 (100)	1/1 (100)		Improved cognitive level & social-emotional performance	
Kanai et al., 2017[52]	C	1	Resolution of residual myoclonic seizures after corpus callosotomy				
Landau-Kleffner syndrome							
Benifla et al., 2006[37]	R	1	0/1 (0)				
Park, 2003[68]	R	6	3/6 (50)			Improved alertness & school performance	Decreased
Aicardi syndrome							
Benifla et al., 2006[37]	R	3	0/3 (0)				
Kasasbeh et al., 2014[69]	R	3	1 patient (33%) had “significant, sustained” improvement				
Angelman syndrome							
Danielsson et al., 2008[38]	P	1	0/1 (0)			Discrete improvement in mental age	
Kokoszka et al., 2017[55]	R	1	Rare, disabling Engel class IIB seizures (almost seizure free)				
Tomei et al., 2018[70]	C	3	Unspecified seizure reduction			Improved alertness, interaction, attention, & school performance	

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TABLE 2. Outcomes of VNS treatment in pediatric patients with genetic etiologies of DRE

Study Characteristics			Primary Outcomes (no. [%])			Secondary Outcomes	
Authors & Year	Study Type	No. of Pediatric Patients	≥50% Seizure Reduction Rate	Seizure Freedom Rate	≥90% Seizure Reduction Rate	Cognitive, Functional, & Behavioral Improvements	Seizure Severity
r(20)							
Alpman et al., 2005[71]	C	1	0/1 (0)				
Chawla et al., 2002[72]	C	1	1/1 (100)	1/1 (100)		Increased alertness & decreased lethargy; verbalization in a previously nonverbal patient	
Herrgård et al., 2007[73]	C	1	0/1 (0)				
Lissencephaly							
Benifla et al., 2006[37]	R	2	2/2 (100)				
Shahwan et al., 2009[35]	R	1	1/1 (100)				Resolution of SE & drop attacks

C = case report; GTC = generalized tonic-clonic; MERRF = mitochondrial encephalomyelopathy with ragged-red fibers; P = prospective cohort study; R = retrospective cohort study; SE = status epilepticus.

* The responder rate was calculated on the basis of a subset analysis of DS patients with predominantly GTC seizures.

† The responder rate was calculated on the basis of only reduction in GTC seizures.

response. Although much is still unclear, increased genetic testing of children with epilepsy and large, prospective, long-term follow-up studies of specific genetic etiologies of DRE may help elucidate specific seizure freedom and response rates over time.

Broader Implications

VNS may have meaningful benefit in terms of seizure control. Epilepsy surgery has been shown to reduce healthcare utilization, emergency department visits, inpatient stays, and use of antiepileptic drugs in children, thereby reducing morbidity and mortality rates when compared with medical management.[60] VNS may be associated with decreased healthcare costs in the long term,[61–63] despite initially higher periprocedural costs inclusive of implant costs.[64] In addition to decreased healthcare utilization and decreased costs from a systems standpoint, decreased healthcare utilization improves QOL for both patients and caregivers.[3] Furthermore, improved QOL outcomes of VNS therapy have been reported irrespective of seizure reduction,[62,65] with many positive impacts of VNS on cognition, behavior, and psychosocial outcomes identified in our review. These benefits may support exploration of the use of VNS earlier in the treatment of DRE, even if significant seizure reduction is not attained.

VNS implantation at a younger age predicts better outcomes, including sustained VNS efficacy and achievement of seizure freedom.[16,36] A meta-analysis found that patients < 6 years old had the most dramatic benefit in seizure reduction.[18] In patients < 3 years old, successful treatment may be attributed to increased neuroplasticity.[46] Initiation of therapy to control seizures in young children with still developing brains may allow faster recovery, and development of circuitry via plasticity may foster improved neurocognitive, behavioral, functional, and seizure outcomes. Determination of which genetic subgroups of patients are responsive to VNS may allow providers to accelerate referrals to surgical epilepsy centers where children can be treated at an earlier age when appropriate.

Future Directions

At least 500 epilepsy-associated genes have been detected since 1995, though many are not well defined and are of unclear significance.[66] However, despite advancements in rapid next-generation sequencing, over 50% of patients remain without a genetic diagnosis.[67] Furthermore, genetic testing is not always widely available, accessible, or covered by insurance, further impeding diagnosis of genetic etiologies of DRE. As technology improves and becomes more commonplace, our understanding of genetic etiologies of epilepsy will grow, necessitating a deeper understanding and characterization of the underlying molecular basis of epilepsy.[67] Moreover, more robust use of genetic testing in the clinical setting may improve genetic diagnosis and allow further study of etiology-specific treatment outcomes. By characterizing the reported responses to VNS in patients with different etiologies of genetic epilepsy, we can improve access in order to at least palliate seizure burden and to optimize outcomes in affected children who otherwise have no known cure at present. The promise of precision medicine, personalized medicine, and gene therapy will change the discussion to come, but such potential is beyond the scope of this review.

Limitations

There were several limitations in this study. We included only published studies with the full text available, thereby risking publication bias. Studies that show no impact of VNS treatment may be underrepresented in the literature, causing our results to overestimate the number of significant study results. Additionally, this systematic review was based on moderate-quality evidence owing to the lack of randomized trials, and some included studies were at risk of bias due to their retrospective nature. The

TABLE 3. Summary of all studies included in the current review

Authors & Year	Design	Evidence Level	Total No. of Patients	No. of Included Patients*	Genetic Etiology (no. of patients)	Key Findings & VNS Outcomes
TSC						
Elliott et al., 2009[22]	R	B	12	8	TSC (8)	Responder rate was 87.5% (7/8 patients). Mean (range) seizure reduction was 71% (12.5–100%). >90% seizure reduction in 2 patients, w/ seizure freedom in 1. 4/7 responders (57%) had decreased ictal/postictal severity. Improved development & behavior were observed.
Hosain et al., 2000[39]	P	B	13	2	TSC (2)	1 patient had 93% seizure reduction. The 2nd patient had 37% seizure reduction.
Lagae et al., 2015[16]	P	B	70	4	TSC (4)	75% (3/4) of patients achieved seizure freedom, all aged <5 yrs. No other etiology correlated w/ VNS efficacy. Statistically significant correlation btwn seizure freedom & younger age at implantation (<5 yrs). Sustained VNS efficacy was more likely to occur in younger children or children w/ shorter epilepsy duration prior to VNS.
Major & Thiele, 2008[21]	R	B	16	12	TSC (12) (*TSC1* [4] & *TSC2* [7])	Responder rate was 50% (6/12 patients). >90% seizure reduction in 2 patients. All responders had decreased ictal/postictal severity. Improved alertness, behavior, & development were observed. No significant association btwn TSC mutation & VNS outcomes.
Mikati et al., 2009[41]	R	B	16	1	TSC (1)	Patient experienced 31.8% reduction in seizure frequency. Seizures had milder severity but longer duration.
Nagarajan et al., 2002[42]	R	B	16	1	TSC (1)	Patient experienced <25% reduction in seizure frequency. Seizures had decreased severity.
Overwater et al., 2015[43]	R	B	71	1	TSC (1)	Patient did not experience any improvement in seizure frequency.
Parain et al., 2001[44]	R	B	10	8	TSC (8)	Responder rate was 87.5% (7/8 patients). >90% seizure reduction in 5 patients. Decreased seizure intensity, briefer seizure duration, & increased alertness were observed.
Zamponi et al., 2002[45]	P	B	13	1	TSC (1)	Patient experienced 70% reduction in seizure frequency.
Zamponi et al., 2008[46]	R	B	6	1	TSC (1)	Early seizure reduction of 40%, w/ eventual seizure freedom. Improved alertness & social interaction were observed. Authors concluded that VNS implantation at a young age (<3 yrs) can be successful owing to increased plasticity.
Zamponi et al., 2010[23]	R	B	11	9	*TSC2* (9)	Responder rate was 77.8% (7/9 patients). Mean (range) seizure reduction was 61% (33–99%). 4/7 responders (57%) had decreased ictal/postictal severity. 3/4 patients w/ drop attacks had decreased intensity. Significant reduction of aggressive behaviors in all patients. 2/9 patients had increased cognitive level (both aged <6 yrs). Patients who underwent implantation at younger ages (<6 years) had the greatest benefit in adaptive behaviors, particularly communication.
DS						
Bremer et al., 2012[29]	R	B	22	13	DS (13)	*SCN1A* gene mutations or deletions were found in 15/22 children (68%). 1/13 patients (7.7%) was a responder to the VNS implant.
Caraballo, 2011[30]	R	B	59	3	DS (3)	Responder rate was 66.7% (2/3 patients), w/ no improvement in the 3rd patient. EEG abnormalities improved in the 2 responders after 1 yr of VNS.
Chen et al., 2012[27]	R	B	8	1	DS (1)	Patient experienced >90% reduction in seizure frequency.
Dlouhy et al., 2016[32]	R	B	7	6	DS (6)	Responder rate was 66.7% (4/6 patients) w/ no improvement in 1 patient.
Fernandez et al., 2015[75]	R	B	15	3	DS (3)	All 3 patients had improved seizure frequency, although none became seizure free. All 3 patients had multiple episodes of SE prior to VNS, which resolved w/in 12 mos. Improvement in seizure frequency was not associated w/ any etiology.

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TABLE 3. Summary of all studies included in the current review

Authors & Year	Design	Evidence Level	Total No. of Patients	No. of Included Patients*	Genetic Etiology (no. of patients)	Key Findings & VNS Outcomes
DS (*continued*)						
Fulton et al., 2017[25]	R	B	20	20	*SCN1A* mutation (20) (either DS or borderline SMEI)	Responder rate was 65% (13/20 patients) for those w/ GTC seizures only. Of 12 patients at authors' institution, 9/12 (75%) were responders (GTC seizures); 4/9 responders had improved cognition & speech & 7/9 had >75% reduction in seizures. Of 8 patients treated at outside institution, 4/8 (50%) were responders.
Orosz et al., 2014[15]	R	B	347	20	DS (20)	At 12 mos post-VNS implantation, subset analysis showed that only 25% (5/20) of DS patients w/ predominantly GTC seizures were responders vs 37.6% (130/346) of the entire study population.
Sirsi et al., 2016[26]	R	B	8	8	DS (8) (mutation [2], unclear variant [4], or whole-gene deletion [1] of *SCN1A*)	Responder rate was 37.5% (3/8 patients). 50% (4/8) of patients had no significant improvement. 1 nonresponder had decreased seizure duration, decreased SE, & improved QOL. Patient w/ disease-causing whole-gene deletion had the best response to VNS (>75% improvement).
Zamponi et al., 2011[6]	R	B	8	7	DS (7)	Responder rate was 57.1% (4/7 patients), w/ no improvement in 3 patients. Mean (range) seizure reduction was 30.6% (0–61%). In all patients, cognitive level was unchanged after 1 yr of VNS. 1 patient had clinically significant improvement in adaptive behaviors, particularly communication. Slight improvement in alertness & communicative skills in all patients.
MD						
Arthur et al., 2007[9]	R	B	5	5	ETC deficiency (5)	No patients had a common mitochondrial DNA mutation. All 5 children were considered nonresponders to VNS.
Blount et al., 2006[49]	R	B	6	1	Unspecified (1)	Patient (<5 yrs) w/ history of multiple GTC seizures nightly reduced to 1 seizure per night that was shorter in duration & less intense.
Fujimoto et al., 2012[48]	C	E	2	1	Progressive myoclonic epilepsy (MERRF) (1)	Patient achieved seizure freedom. No improvement in cognitive level, myoclonus, or cerebellar symptoms.
Nolan et al., 2019[50]	C	E	1	1	*DNM1L* variant (pathogenic) (1)	VNS was placed after hemispherectomy, resulting in decreased seizure frequency. Device required removal due to sinus bradycardia & 1st-degree atrioventricular block.
Rett syndrome						
Hornig et al., 1997[51]	P	B	19	1	Rett syndrome (1)	Patient experienced 30% reduction in seizure frequency.
Wilfong & Schultz, 2006[8]	R	B	7	7	Rett syndrome (7) (classic *MECP2*+ [5] & atypical *MECP2*– [2] syndrome)	Responder rate at 12 mos was 85.7% (6/7 patients). 4/7 had ≥90% reduction at 12 mos. Increased alertness was observed in all patients but no change in mood or communicative skills.
r(20)						
Alpman et al., 2005[71]	C	E	1	1	r(20) (1)	Early 50% seizure reduction; this improvement was not maintained.
Chawla et al., 2002[72]	C	E	1	1	r(20) (1)	Early dramatic seizure reduction w/ eventual seizure freedom. Increased alertness & decreased lethargy were observed. Patient was able to start verbalizing despite being previously nonverbal.
Herrgård et al., 2007[73]	C	E	3	1	r(20) (1)	Patient experienced 25% reduction in seizure frequency.

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Authors & Year	Design	Evidence Level	Total No. of Patients	No. of Included Patients*	Genetic Etiology (no. of patients)	Key Findings & VNS Outcomes
Doose syndrome						
Parker et al., 1999[54]	P	B	16	2	Doose syndrome (2)	67% seizure reduction in 1 patient but no improvement in the other.
Fan et al., 2014[53]	C	E	1	1	Doose syndrome (1)	Patient achieved seizure freedom. Increased cognitive level & social-emotional performance were observed.
Kanai et al., 2017[52]	C	E	1	1	Doose syndrome (1)	VNS implantation led to complete resolution of residual myoclonic seizures after corpus callosotomy.
Multiple disorders/other disorders						
Alexopoulos et al., 2006[36]	R	B	46	6	TSC (3), unspecified MD (2), & Rett syndrome (1)	All TSC patients were responders (>50% reduction, >75% reduction, & seizure freedom). The Rett patient was a responder (>50% seizure reduction). Both MD patients were nonresponders (<50% reduction). Younger patients (<12 yrs) appeared to have a better response to VNS than older pediatrics patients.
Baba et al., 2017[74]	C	E	1	1	*CDKL5* mutation (1)	Seizure frequency reduced from numerous seizures per day to weekly. Improved alertness, concentration, & energy were observed.
Benifla et al., 2006[37]	R	B	41	10	TSC (2), Aicardi syndrome (3), lissencephaly (2), Coffin-Siris syndrome (1), Landau-Kleffner syndrome (1), & Mosaic Turner syndrome (1)	1 TSC patient (1/2) was a responder (>50% seizure reduction). None of the Aicardi syndrome patients were responders. Both lissencephaly patients were responders. The 1 Coffin-Siris syndrome patient had >50% reduction. The 1 Mosaic Turner syndrome patient had >50% reduction. The 1 Landau-Kleffner syndrome patient had <50% reduction.
Cersósimo et al., 2011[31]	R	B	64	6	DS (3) & Doose syndrome (3)	1 DS patient (1/3) was a responder. Another had <50% seizure reduction. Both had improved ictal/postictal severity. The 3rd patient had no improvement. 2 Doose syndrome patients (2/3) were responders. Another patient had <50% seizure reduction. All 3 had improved ictal/postictal severity. All patients who responded well to VNS had improved mental age.
Danielsson et al., 2008[38]	P	B	8	2	TSC (1) & Angelman syndrome (1)	The TSC patient had no change in seizure frequency but improved social interaction. The Angelman syndrome patient had no change in seizure frequency but discrete improvement in mental age. Improved attention span in both patients (concurrent ASD & ADHD) but not enough to alter diagnosis. No improvement in IQ or DQ.
Kang et al., 2006[40]	P	B	16	3	TSC (2) & unspecified MD (1)	1 TSC patient had >90% seizure reduction; the other achieved seizure freedom. The 1 MD patient had no improvement.
Kasasbeh et al., 2014[69]	R	B	4	3	Aicardi syndrome (3)	Only 1 patient (1/3) had significant, sustained improvement in seizure control. Another patient had worsening seizure control.
Kokoszka et al., 2017[55]	R	B	56	3	*SCN1A* mutation (1), Angelman syndrome (1), & Down syndrome (1)	1 patient w/ *SCN1A* mutation had worthwhile seizure reduction (Engel class IIIA) due to VNS implantation after temporal lobectomy failed to achieve seizure freedom. The 1 Angelman syndrome patient had rare disabling post-VNS seizures (Engel IIB), i.e., "almost seizure free." The 1 patient w/ Down syndrome had worthwhile seizure reduction (Engel IIIA) due to VNS implantation after nonfocal seizures persisted despite corpus callosotomy.

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TABLE 3. Summary of all studies included in the current review

Authors & Year	Design	Evidence Level	Total No. of Patients	No. of Included Patients*	Genetic Etiology (no. of patients)	Key Findings & VNS Outcomes
Multiple disorders/other disorders (*continued*)						
Lund et al., 2011[33]	R	B	50	5	TSC (3), DS (1), & Rett syndrome (1)	2/3 TSC patients had <50% seizure reduction; 1 had no improvement. There was <50% reduction in the 1 DS patient & 1 Rett syndrome patient.
Majoie et al., 2005[34]	P	B	19	5	SBH (1), DS (2), & Doose syndrome (2)	The 1 patient w/ SBH had <50% seizure reduction. Both Doose syndrome patients were responders; 1 had >90% reduction. 1 DS patient had no improvement; the 2nd patient had increased seizures.
Park, 2003[68]	R	B	65	6	Landau-Kleffner syndrome (6)	Responder rate was 50% (3/6 patients) at 6-mo follow-up. Improved alertness, postictal severity, school performance, & overall QOL were observed.
Rossignol et al., 2009[28]	P	B	28	3	DS (2) & Doose syndrome (1)	1 DS patient had 90% seizure reduction; the 2nd had no improvement. The 1 Doose syndrome patient achieved seizure freedom. No patient had change in cognitive function.
Shahwan et al., 2009[35]	R	B	26	5	TSC (2), DS (2), & lissencephaly (1)	Both TSC patients were responders: 1 became seizure free, and the other had longer periods of seizure freedom. 1 DS patient was a responder w/ resolution of SE & briefer seizures; the 2nd did not respond. The patient with lissencephaly had >75% seizure reduction & resolution of SE & drop attacks.
Tomei et al., 2018[70]	C	E	3	3	Angelman syndrome (3)	Improved alertness, interaction, attention, school performance, & QOL were observed. All 3 patients had decreased seizure burden.
Zamponi et al., 2011[47]	R	B	39	3	TSC (2) & Rett syndrome (1)	One TSC patient had 70% seizure reduction; the 2nd had 65% seizure reduction. The Rett syndrome patient experienced a 50% reduction in seizure frequency.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DQ = developmental quotient; ETC = electron transport chain; IQ = intelligence quotient; SBH = subcortical band heterotopia; SMEI = severe myoclonic epilepsy of infancy.
* The patients reported in each study were included in our results only if they met the inclusion criteria.

included studies also analyzed different numbers of pediatric patients with each genetic etiology and subtype, precluding us from determining uniform response rates for the patients with each genetic etiology who were treated with VNS and reported in the literature. Many studies included patients with genetic etiologies of DRE who could not be included owing to the inability to differentiate pediatric from nonpediatric cases. Strict adherence to our study population and inclusion and exclusion criteria was essential, and therefore, some potentially useful studies with data from additional patients could not be analyzed in this review. Furthermore, only studies written in or translated to the English language were included, and perhaps studies from other regions that demonstrated effectiveness were excluded. Nevertheless, this systematic review provides an important starting point on this topic and has potential to inform future studies.

Conclusions

We conducted a systematic review of VNS outcomes in pediatric patients with genetic etiologies of DRE and found that TSC and DS were among the most studied etiologies. TSC patients had substantial seizure reduction and improvements in QOL, whereas DS patients had less robust reduction with QOL benefits. A limited number of patients with several other etiologies—including mitochondrial disorders, Rett syndrome, Doose syndrome, Landau-Kleffner syndrome, Aicardi syndrome, Angelman syndrome, ring chromosome 20 syndrome, and lissencephaly—had variable responses. We have presented a starting point for the study of etiology-specific outcomes of VNS in children with genetically associated DRE. Increased genetic testing and diagnosis of epilepsy, alongside long-term follow-up studies, may continue to better characterize response to VNS and optimize outcomes in these children.

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Disclosures

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Author Contributions

Conception and design: Lam, LoPresti. Acquisition of data: Hajtovic, LoPresti. Analysis and interpretation of data: Hajtovic, LoPresti, Zhang. Drafting the article: Hajtovic, LoPresti. Critically revising the article: Lam, Hajtovic, LoPresti, Katlowitz, Kizek. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lam. Statistical analysis: Zhang. Administrative/technical/material support: Lam, LoPresti. Study supervision: Lam.

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