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CRITICAL REVIEW – INVITED COMMENTARY

The role of surgery in the management of Lennox–Gastaut syndrome: A systematic review and meta-analysis of the clinical evidence

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Abstract

Lennox–Gastaut syndrome (LGS) is a severe form of childhood onset epilepsy in which patients require multiple medications and may be candidates for palliative surgical intervention. In this meta-analysis, we sought to evaluate the impact of palliative vagus nerve stimulation (VNS), corpus callosotomy (CC), and resective surgery (RS) by analyzing their impact on seizure control, antiepileptic drug (AED) usage, quality of life (QOL), behavior, cognition, prognostic factors, and complications. A systematic search of PubMed MEDLINE, Scopus, and Cochrane Database of Systematic Reviews was performed to find articles that met the following criteria: (1) prospective/retrospective study with original data, (2) at least one LGS surgery patient aged less than 18 years, and (3) information on seizure frequency reduction (measured as percentage, Engel class, or qualitative comment). Seizures were analyzed quantitatively in a meta-analysis of proportions and a random-effects model, whereas other outcomes were analyzed qualitatively. Forty studies with 892 LGS patients met the selection criteria, with 19 reporting on CC, 17 on VNS, four on RS, two on RS + CC, one on CC + VNS, and one on deep brain stimulation. CC seizure reduction rate was 74.1% (95% confidence interval [CI] = 64.5%–83.7%), and VNS was 54.6% (95% CI = 42.9%–66.3%), which was significantly different ($p < .001$). RS seizure reduction was 88.9% (95% CI = 66.1%–99.7%). Many VNS patients reported alertness improvements, and most had no major complications. VNS was most effective for atonic/tonic seizures; higher stimulation settings correlated with better outcomes. CC patients reported moderate cognitive and QOL improvements; disconnection syndrome, transient weakness, and respiratory complications were noted. Greater callosotomy extent correlated with better outcomes. AED usage most often did not change after surgery. RS showed considerable QOL improvements for patients with localized seizure foci. In the reported literature, CC appeared to be more effective than VNS for seizure reduction. VNS may provide a similar or higher level of QOL improvement with lower aggregate risk of complications. Patient selection, anatomy, and seizure type will inform decision-making.

KEYWORDS
corpus callosotomy, epilepsy surgery, resective surgery, seizures, vagus nerve stimulation

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a severe form of epilepsy that typically presents during early childhood and is estimated to encompass 1%–10% of all childhood epilepsy cases.[1–6] Complete seizure control in LGS is unfortunately not possible, and all patients experience intellectual and psychosocial dysfunction as a result.[1,7,8] Behavioral problems may also result from epilepsy, with patients exhibiting attention deficit disorder and aggression.[1,9] Seizure reduction is a priority in the treatment of LGS due to the potential to improve symptoms, cognitive problems, behavioral issues, and overall quality of life (QOL).[10] The major goal for seizure control has been to reduce the frequency and intensity of seizures overall, with special focus on the most injurious seizures such as drop attacks and tonic–clonic seizures.[11]

Various treatment strategies have been employed to reduce seizures in LGS patients. Antiseizure medications (ASMs) have some efficacy in reducing although rarely eliminating seizures.[11–16] LGS is inevitably drug-resistant, and the chronic use of ASMs has been associated with poor prognosis.[17] Because medical treatment typically fails to control seizures in LGS patients, a surgical workup should be considered early in the management of disease.[17] For patients with identifiable seizure foci on imaging, resective surgery (e.g., lobar resection or hemispherectomy) has been shown to successfully control seizures.[18] There have also been reports of favorable resective surgery outcomes even when epileptiform discharges originated from more than one brain area.[17–19] Of note, there have been descriptions of lower efficacy for resective surgery for long-term seizure control,[20] but other studies appear to be more promising.[21–25]

Whereas resective surgery is thought of as possibly "curative," two other "palliative" surgical options, corpus callosotomy (CC) and vagus nerve stimulation (VNS), are also considered for LGS patients, especially when epileptiform discharges are not easily localized.[17] CC has been shown to reduce tonic, atonic, and tonic–clonic seizure types in LGS,[26] but poses risks of disconnection syndrome, venous infarction, bleeding, and neuropsychological deficits.[27] VNS, as a less invasive approach, has generally been considered not to be as risky as CC,[28] with documented complications such as voice alteration, drooling, coughing, and dyspnea.[28,29] However, one meta-analysis found that VNS was less effective for atonic seizure reduction in LGS patients in comparison to CC.[30] The relative risks and benefits of these interventions need to be further elucidated.

Key Points

- LGS patients with localized seizure foci may benefit greatly from resective surgery
- Seizures in LGS may be better controlled by CC than VNS, but VNS may provide similar QOL benefits with lower risk of adverse events
- Combination surgeries have varying levels of efficacy, with resective surgery + CC showing the most promise for a subset of LGS patients

Previous reviews/meta-analyses that have investigated surgical interventions in LGS have quantitatively compared the relative efficacy of VNS and CC for seizure reduction[30] and commentated broadly on the qualitative risks and benefits of various surgical procedures.[17,31,32] In this meta-analysis, we sought to evaluate the role of epilepsy surgery in management of LGS by (1) evaluating the clinical impact of surgery, (2) summarizing prognostic factors, and (3) quantitatively analyzing the efficacy of surgical procedures.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[33] guidelines was conducted to investigate the different surgical treatments for LGS patients. PubMed MEDLINE and Scopus were systematically searched for English-language studies with no date limits applied. The PICO framework was used to search for articles. The search terms encompassed all combinations of (1) Lennox–Gastaut syndrome, Lennox–Gastaut, LGS, and Lennox; and (2) corpus callosotomy, callosotomy, commissurotomy, vagus nerve stimulation, vagal nerve stimulation, VNS, epilepsy surgery, resective surgery, and neuromodulation.

2.2 | Selection criteria

Inclusion criteria included (1) prospective or retrospective study with original data, (2) at least one pediatric (<18 years of age) LGS patient treated with surgery, (3) mean age of surgically treated LGS patients less than

18 years, and (4) information on reduction of seizure frequency (measured as percent seizure reduction, Engel class, or qualitative comment). Exclusion criteria included (1) singular case studies/reports, traditional literature reviews, and theoretical papers; (2) lack of original data; (3) lack of pediatric LGS patients; (4) mean age of LGS patients greater than 18 years and inability to isolate management/outcomes of pediatric LGS patients; (5) lack of any surgical interventions; and (6) lack of information on seizure frequency reduction after intervention. Article relevance, suitability, and quality were evaluated by two authors independently (V.T. and R.D.) using the aforementioned criteria. Disagreements were resolved between the same two authors.

2.3 | Data extraction

From reports that met the inclusion criteria, we extracted the following information from each study: authors, number of LGS patients, age of LGS patients at surgery, comparison/control groups, study design, study year, surgical intervention(s), seizure outcomes at 0–6 months/6 months–2 years/2+ years postprocedure, seizure outcomes at last follow-up with most data, qualitative evidence of seizure outcomes, intellectual outcomes, evidence of QOL changes/improvements, evidence of complications, and prognostic factors of better or worse outcomes. Seizure reduction outcomes for patients were treated as binary: positive or negative. Patients were classified as having positive seizure outcomes if they were described as having greater than 50% seizure reduction, being in Engel Class I–III, or qualitatively described as having "significant," "considerable," or "worthwhile" seizure reduction. For studies with patients listed individually, outcomes were aggregated to represent the study in our analysis. The primary outcome of interest was seizure reduction rate at the last follow-up with most data, as we wanted to best evaluate long-term seizure reduction for each intervention while also preserving a large pooled sample size. Secondary outcomes of interest included seizure reduction rates at various postprocedure follow-up times (0–6 months, 6 months–2 years, and after 2 years), QOL measures, and complications. Not all studies possessed complete data for the fields described above.

2.4 | Quality assessment

The quality of evidence was evaluated according to the Cochrane ROBINS-I guidelines.[34] Publication bias was evaluated by conducting a linear regression test of funnel plot asymmetry.

2.5 | Statistical analysis for seizure reduction rates

Cohorts were grouped for quantitative analysis based on treatment modality: VNS, CC, and resective surgery. Given the small number of studies assessing resective surgery + CC, VNS + CC, and deep brain stimulation (DBS), these studies were not subjected to quantitative meta-analysis. For the three surgical interventions included in the meta-analysis, four outcomes were assessed: seizure reduction rate at last follow-up, seizure reduction rate at 0–6 months postprocedure, seizure reduction rate at 6 months–2 years postprocedure, and seizure reduction rate at 2+ years postprocedure. Seizure reduction rate at last follow-up included all studies, whereas the other outcomes used a smaller subset of the studies within each intervention due to incomplete data. Seizure reduction rate was delineated as a proportion based on the study sample size. Odds ratios were not calculated, as most studies did not include a control group for comparison.

A random-effects model was used to calculate pooled proportions with 95% confidence intervals (CIs) for the last follow-up data. Raw pooled proportions and 95% CIs were calculated for the other time points. For groups of studies with a mean pooled proportion between .2 and .8, the inverse variance method was used to calculate weights. The Tau^2 value for study heterogeneity was calculated using a DerSimonian–Laird estimator, and the proportions were left untransformed. For groups of studies with a mean pooled proportion less than .2 or more than .8, a logit transformation was used for proportions and Tau^2 was calculated using a maximum-likelihood estimator. Study heterogeneity was also measured by the I^2 statistic for all plots. Visual evaluation of funnel plots and Begg and Mazumdar test were used to assess publication bias.

Two-proportion z-tests were used to compare pooled proportions. A p-value $\leq .05$ was considered to be statistically significant. All statistical analyses were performed using R, version 4.0.1.

3 | RESULTS

Using the search strategy detailed above, 519 articles were initially identified, and 40 were included in this systematic review (Figure 1, Table 1). All studies were published between 1990 and 2020. There were 28 retrospective studies (70%) and 12 prospective studies (30%). The 40 studies assessed 44 intervention groups, of which there were 19 CC,[24,28,35–51] 17 VNS,[28,29,36,52–65] four resective surgery,[21,22,25,66] two resective surgery + CC,[22,25] one CC + VNS,[67] and one DBS.[68] There were, in total, 892 LGS patients evaluated, with a breakdown by intervention of 337 CC, 370 VNS, 138

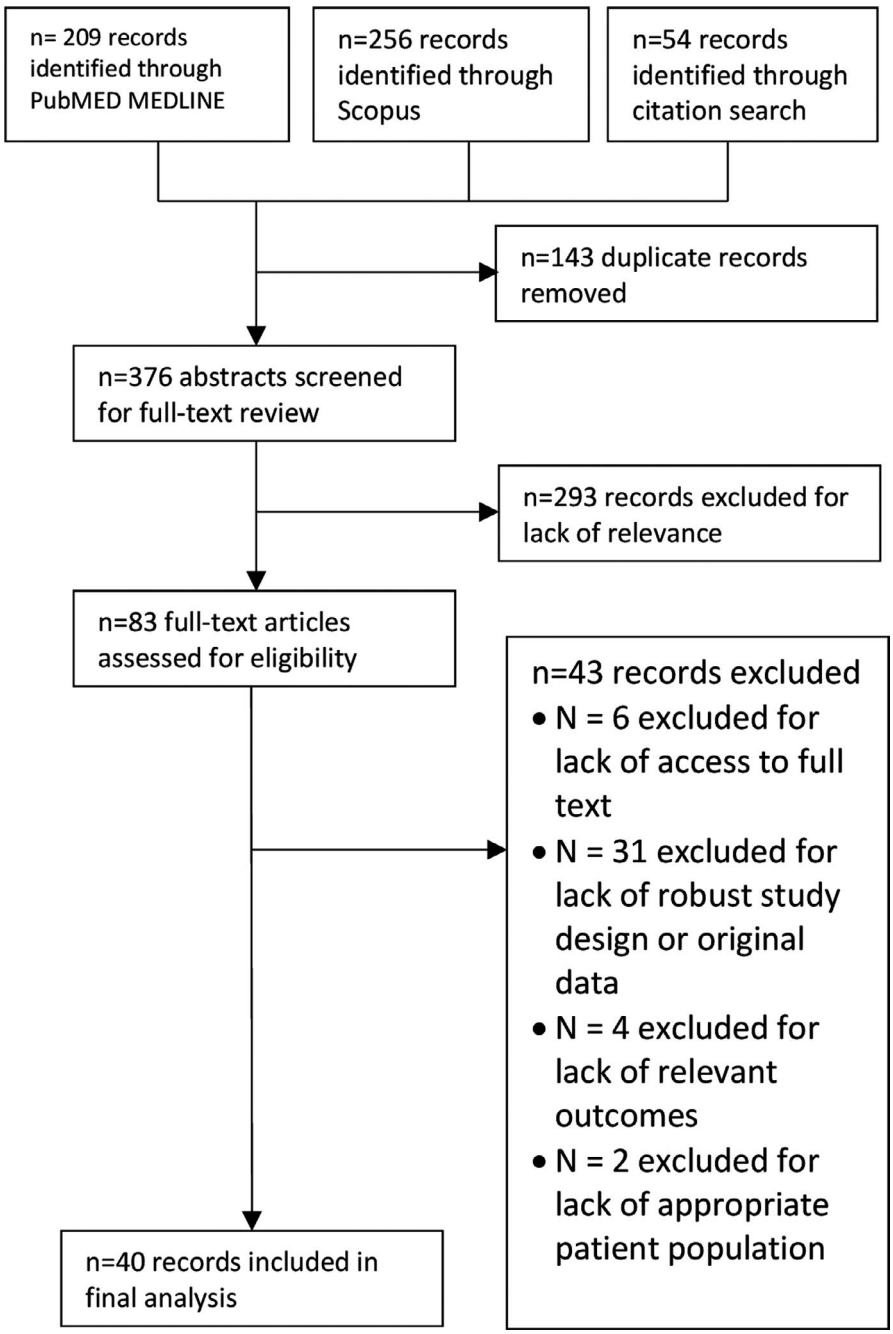

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart

resective surgery, 25 resective surgery + CC, nine CC + VNS, and 13 DBS.

3.1 | Impact of surgical treatment on antiepileptic drugs

Thirty-one studies assessing 33 intervention groups commented on usage of antiepileptic drugs (AEDs) before surgery, during the study period, and/or after surgery. Most patients appeared to have been on 1–5 AEDs prior to surgery, although the efficacy of these drugs was in question given the choice to move to surgery. Many studies reported a mean or median close to three AEDs prior to surgery.[28,35,38,43,44,47,52–54,59,60,62,65,67] All 17 VNS studies commented on AED usage, and among these, 0 reported an overall increase in AEDs after surgery for their patients (0%), four overall decrease in AED (23.5%), nine very little or no change (53%), and four unspecified change (23.5%). Eleven CC studies commented on AED usage, and among these, two reported an overall increase in AEDs after surgery for their patients (18%), five overall decrease in AED (45%), three very little or no change (27%), and one unspecified change (9%). Among the other interventions, one resective surgery study reported a notable decrease in AEDs after surgery, whereas the others reported very little change or did not specify.

TABLE 1 Characteristics of all 40 included studies

Authors	Year	Interventions assessed	Country	Comparison groups	Risk of bias	LGS patients, *n*	Outcomes of interest	Reported adverse events	QOL evaluation
Aldenkamp et al.	2002	VNS	Netherlands	Different follow-up points of VNS treatment	Moderate	19	Seizures, QOL, AED	N/A	Provider assessment using Dutch scales
Ben-Menachem et al.	1999	VNS	Sweden	Before and after VNS	Serious	8	Seizures, AED	N/A	N/A
Buoni et al.	2004	VNS	Italy	Before and after VNS	Serious	3	Seizures, complications, AED	No major complications, stimulation related headaches for 1 patient	N/A
Cersósimo et al.	2011	VNS	Argentina	Symptomatic versus cryptogenic for seizure reduction and mental retardation; before and after VNS	Moderate	46	Seizures, QOL, AED	No major complications, some hoarseness, coughing, and change in vocal timbre (cannot be isolated to LGS patients)	Questionnaire
Cukiert et al.	2013	VNS versus CC	Brazil	VNS versus CC	Low	44	Seizures, QOL, complications, AED	VNS: no major complications CC: acute callosal disconnection syndrome, no mortality	QOLIE-31 questionnaire
Frost et al.	2001	VNS	USA	Before and after VNS	Moderate	50	Seizures, QOL, complications, AED	Infection and transient pain at incision site	Provider assessment using unvalidated 5-point scale
Hallböök et al.	2005	VNS	Sweden	Before and after VNS	Serious	4	Seizures, QOL, complications, AED	No major complications; some coughing, hoarseness, breath shortness, and transient pain (cannot be isolated to LGS patients)	Parent assessment using visual analogue scale

(Continues)

TABLE 1 (Continued)

Authors	Year	Interventions assessed	Country	Comparison groups	Risk of bias	LGS patients, *n*	Outcomes of interest	Reported adverse events	QOL evaluation
Hornig et al.	1997	VNS	USA	Before and after VNS	Serious	6	Seizures, QOL, AED	N/A	Parent assessment using global evaluation score (indirect proxy)
Hosain et al.	2000	VNS	USA	Before and after VNS	Moderate	13	Seizures, complications, AED	Excessive coughing, infection, hoarseness, change in vocal timbre	N/A
Kostov et al.	2009	VNS	Norway	Before and after VNS	Moderate	30	Seizures, complications, AED	Drooling and voice alteration	N/A
Nagarajan et al.	2002	VNS	Australia	Before and after VNS	Serious	6	Seizures, QOL, complications, AED	No major complications; a few hoarseness and breathing irregularities (cannot be isolated to LGS patients)	Parent assessment using 3-point scale
Lundgren et al.	1998	VNS	Sweden	Before and after VNS	Serious	4	Seizures, QOL, complications, AED	Increased salivation, tiredness, aspiration event, premature current failure	Parent assessment using visual analogue scale
Benifla et al.	2006	VNS	Canada	Before and after VNS	Moderate	10	Seizures, AED	N/A	N/A
Orosz et al.	2014	VNS	European Union	Before and after VNS	Low	146	Seizures, QOL, complications, AED	Convulsion, device damage/removal, infection, dysphonia (cannot be isolated to LGS patients)	Provider assessment of various factors
Shahwan et al.	2009	VNS	Australia	Before and after VNS	Serious	9	Seizures, complications, AED	Agitation at high current for 1 patient	N/A
You et al.	2008	VNS versus CC	South Korea	VNS versus CC	Low	10	Seizures, complications, AED	VNS: dyspnea, drooling CC: aphasia, ataxia, paresis	N/A
Zamponi et al.	2011	VNS	Italy	Before and after VNS, LGS versus SE-MISF	Low	14	Seizures, QOL, complications, AED	No major complications	Parent assessment using Likert scale

(Continues)

TABLE 1 (Continued)

Authors	Year	Interventions assessed	Country	Comparison groups	Risk of bias	LGS patients, *n*	Outcomes of interest	Reported adverse events	QOL evaluation
Jea et al.	2008	CC	Canada	Before and after CC	Serious	5	Seizures, complications	No major complications	N/A
Asadi-Pooya et al.	2013	CC	Iran	Before and after CC	Moderate	18	Seizures, complications, AED	Sepsis/respiratory infection, left-sided hemiparesis, disconnection syndrome, aspiration pneumonia, subcutaneous abscess, prolonged coma	N/A
Chandra et al.	2016	CC	India	CC versus CC + commissurotomy	Low	16	Seizures, complications	No mortality; meningitis, encephalopathy, acute transient disconnection	N/A
Turanli et al.	2006	CC	Turkey	Before and after CC	Serious	5	Seizures, AED	N/A	N/A
Oguni et al.	1991	CC	Canada	Before and after CC	Moderate	14	Seizures, complications	No mortality	N/A
Huang et al.	2019	CC	USA	Before and after CC	Serious	3	Seizures, complications, AED	Transient bradycardia and bigeminy in one patient, and asymptomatic extension of ablation into posterior thalamus in another	N/A
Hur & Kim	2016	CC	South Korea	CC versus resective + CC	Low	10	Seizures	N/A	N/A
Iwasaki et al.	2012	CC	Japan	Before and after CC	Serious	2	Seizures, complications, AED	No surgical complications	N/A
Kwan et al.	2006	CC	Taiwan	LGS w/ West hx versus LGS w/o West hx	Low	74	Seizures	N/A	N/A

(Continues)

TABLE 1 (Continued)

Authors	Year	Interventions assessed	Country	Comparison groups	Risk of bias	LGS patients, *n*	Outcomes of interest	Reported adverse events	QOL evaluation
Jalilian et al.	2010	CC	USA	Complete CC vs two-thirds CC	Moderate	8	Seizures, complications, AED	Transient weakness or speech delays, subgaleal fluid collection w/ peritoneal shunt insertion, transient disconnection syndrome	N/A
Lee et al.	2014	CC, resective	South Korea	LGS versus West	Low	37	Seizures, complications, AED	CC generally lower complications than resective except for transient disconnection syndrome	N/A
Liang et al.	2017	CC	South Korea	Preop electroencephalography versus postop	Low	14	Seizures	N/A	N/A
Liang et al.	2014	CC	China	Medicine versus surgery	Low	23	Seizures, QOL, complications, AED	No mortality, urinary incontinence, aphasia, apraxia	QOLIE-31 questionnaire done by patients w/ aid of caregivers
Lin & Kwan	2012	CC	Taiwan	PRED versus no PRED	Low	48	Seizures	N/A	N/A
Provinciali et al.	1990	CC	Italy	Before and after CC	Serious	2	Seizures	1 patient w/ respiratory complications requiring tracheostomy	N/A
Tanriverdi et al.	2009	CC	Canada	Before and after CC	Moderate	16	Seizures, AED	N/A	N/A
Tao et al.	2020	CC	USA	Before and after CC	Serious	1	Seizures, complications, AED	No complications	N/A
Ding et al.	2016	Resective, resective + CC combo	China	resective versus resective + CC	Low	34	Seizures, complications, AED	No permanent complications or mortality for either resective or resective + CC	N/A

(Continues)

TABLE 1 (Continued)

Authors	Year	Interventions assessed	Country	Comparison groups	Risk of bias	LGS patients, *n*	Outcomes of interest	Reported adverse events	QOL evaluation
Kang et al.	2018	Resective surgery	South Korea	Before and after resective surgery, types of resective surgeries	Moderate	90	Seizures, complications, AED	Minor bleeding	N/A
Liu et al.	2007	Resective, resective + CC combo	China	Before and after resective surgery	Serious	7	Seizures, AED	N/A	N/A
Pati et al.	2013	Resective surgery	USA	Before and after resective surgery	Moderate	21	Seizures	N/A	N/A
Katagiri et al.	2016	CC + VNS combo	Japan	Before and after CC + VNS	Serious	9	Seizures, complications, AED	No mortality; acute disconnection syndrome after CC and some hoarseness/ coughing after VNS	N/A
Velasco et al.	2006	DBS	Mexico	Before and after DBS	Moderate	13	Seizures, complications, AED	Skin erosions	N/A

Abbreviations: AED, antiepileptic drug; CC, corpus callosotomy; combo, combination; DBS, deep brain stimulation; hx, history; LGS, Lennox–Gastaut syndrome; N/A, not available; postop, postoperative; PRED, post-sectional recruitment of epileptiform discharges; Preop, preoperative; QOL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SE-MISF, severe epilepsy with multiple independent spike foci; VNS, vagus nerve stimulation; w/, with; w/o, without.

3.2 | Efficacy of surgical procedures for seizures (meta-analysis)

3.2.1 | Vagus nerve stimulation

Seventeen studies assessed VNS seizure reduction outcomes. At the last follow-up time point with most data, 178 of 370 (raw: 48.1%, random-effects model: 54.6%, 95% CI = 42.9%–66.3%) patients undergoing VNS experienced reduction in seizure frequency (Figure 2). A linear regression test assessing funnel plot asymmetry for the 17 studies revealed no significant publication bias ($p = .24$). Ten studies[28,29,52–59] had seizure reduction data for the 0–6-month postprocedure period, with 128 of 283 (45.2%, 95% CI = 39.5%–51.1%) patients experiencing a reduction in seizure frequency. Eleven studies[28,52–57,59–61,65] had seizure reduction data for the 6-month–2-year postprocedure period, with 125 of 288 (43.4%, 95% CI = 37.8%–49.2%) patients experiencing a reduction in seizure frequency. Nine studies[36,52–54,59,60,62–64] had seizure reduction data for the 2+-year postprocedure period, with 94 of 185 (50.8%, 95% CI = 43.7%–57.9%) patients experiencing a reduction in seizure frequency. Two-proportion z-tests revealed no significant differences between seizure reduction at 0–6 months and 6 months–2 years ($p = .72$), 0–6 months and 2+ years ($p = .28$), or 6 months–2 years and 2+ years ($p = .14$).

3.2.2 | Corpus callosotomy

Nineteen studies assessed CC seizure reduction outcomes. At the last follow-up time point with most data, 227 of 337 (raw: 66.3%, random-effects model: 74.1%, 95% CI = 64.5%–83.7%) patients undergoing CC experienced a reduction in seizure frequency (Figure 3). A linear regression test assessing funnel plot asymmetry for the 19 studies revealed no significant publication bias ($p = .52$). Eight studies[28,37,39,41,42,44–46] had seizure reduction data for the 0–6-month postprocedure period, with 87 of 125 (69.6%, 95% CI = 61.5%–77.7%) patients experiencing a reduction in seizure frequency. Ten studies[28,35,37,38,41,42,44,45,47,49] had seizure reduction data for the 6-month–2-year postprocedure period, with 103 of 152 (67.7%, 95% CI = 60.0%–75.4%) patients experiencing a reduction in seizure frequency. Thirteen studies[24,35–38,40–44,48,50,51] had seizure reduction data for the 2+-year postprocedure period, with 193 of 291 (66.3%, 95% CI = 61.1%–71.5%) patients experiencing a reduction in seizure frequency. Two-proportion

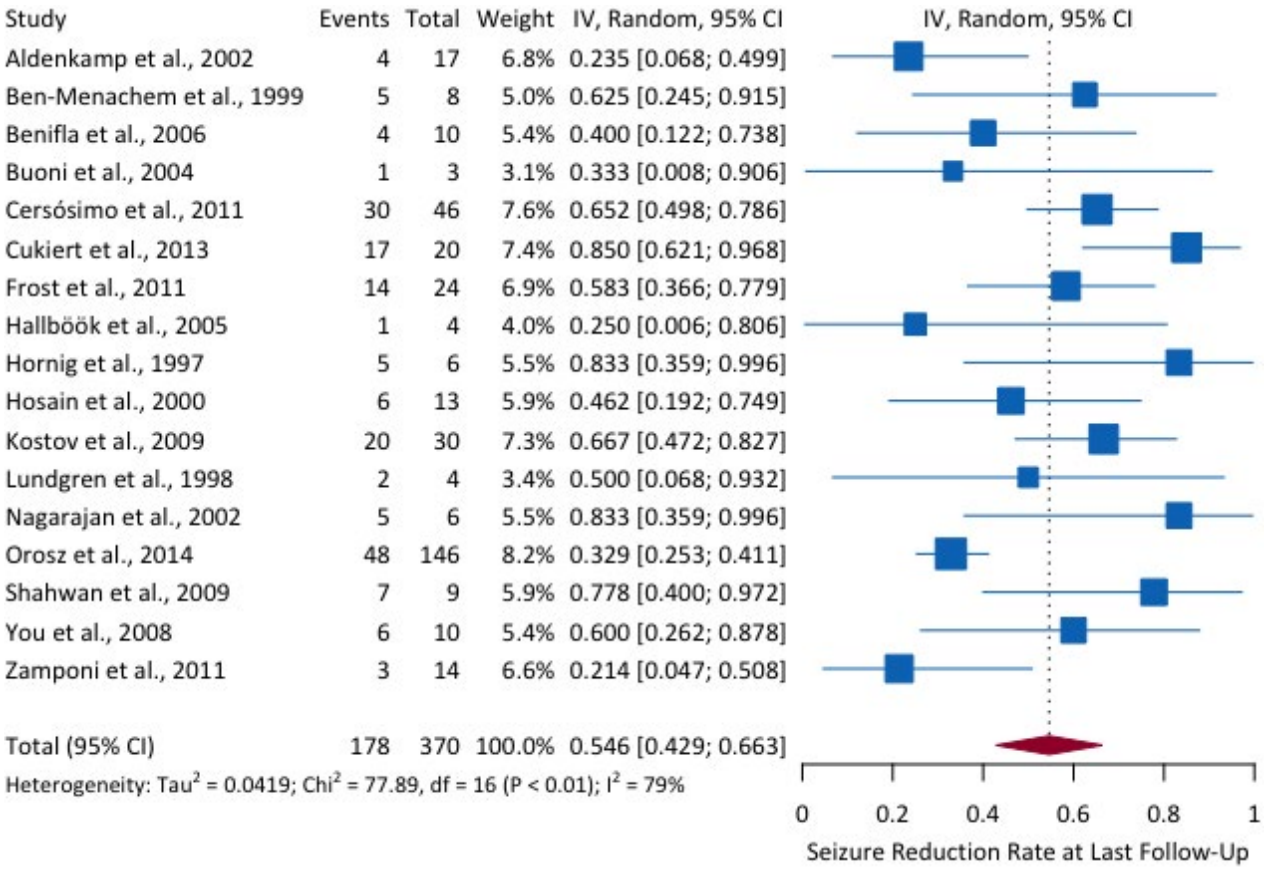

FIGURE 2 Forest plot of last follow-up seizure reduction rate with the most data for vagus nerve stimulation studies. CI, confidence interval; IV, untransformed proportion

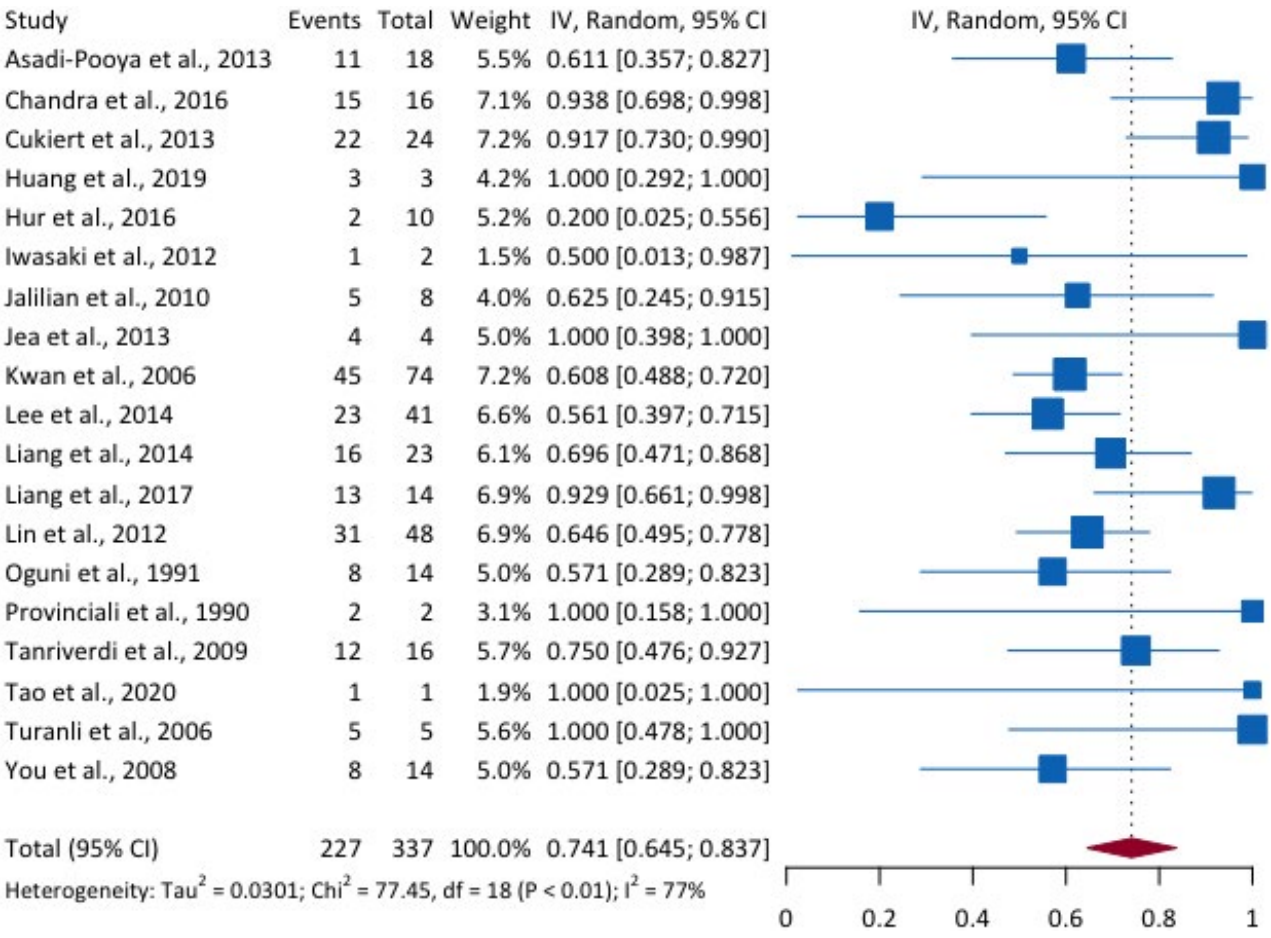

FIGURE 3 Forest plot of last follow-up seizure reduction rate with the most data for corpus callosotomy studies. CI, confidence interval; IV, untransformed proportion

z-tests revealed no significant differences between seizure reduction at 0–6 months and 6 months–2 years ($p = .84$), 0–6 months and 2+ years ($p = .59$), or 6 months–2 years and 2+ years ($p = .84$).

3.2.3 | VNS versus CC

Both VNS and CC were compared directly, as they represent palliative options for surgery. Two-proportion *z*-tests revealed significant differences between seizure reduction rates for VNS and CC at the last follow-up time point (48.1% vs. 66.3%, $p < .001$), 0–6-month postprocedure period (45.2% vs. 69.6%, $p < .001$), 6-month–2-year postprocedure period (43.4% vs. 67.7%, $p < .001$), and 2+-year postprocedure period (50.8% vs. 66.3%, $p = .0011$).

3.2.4 | Resective surgery

Four studies assessed resective surgery seizure reduction outcomes. At the last follow-up time point with most data, 105 of 138 (raw: 76.1%, random-effects model: 88.9%, 95% CI = 66.1%–97.1%) patients undergoing resective surgery experienced a reduction in seizure frequency (Figure 4). Publication bias was noted for the four studies via linear regression tests for funnel plot asymmetry ($p = .04$). There were no studies with 0–6-month follow-up information. One study[22] had follow-up information for the 6-month–2-year period, with 17 of 20 (85%) patients experiencing seizure reduction. All four studies had follow-up information at the 2+-year period, which was used to calculate the seizure reduction rate for the last follow-up point category. Two-proportion *z*-tests revealed a significant difference in last follow-up seizure reduction rates between resective surgery and VNS (76.1% vs. 48.1%, $p < .001$) but not between resective surgery and CC (76.1% vs. 67.3%, $p = .076$).

3.2.5 | Combination surgeries and DBS

Two studies assessed resective surgery + CC seizure reduction outcomes. At the last follow-up time point with most data, 22 of 25 (88%, 95% CI = 75.3%–100%) patients undergoing resective surgery + CC experienced a

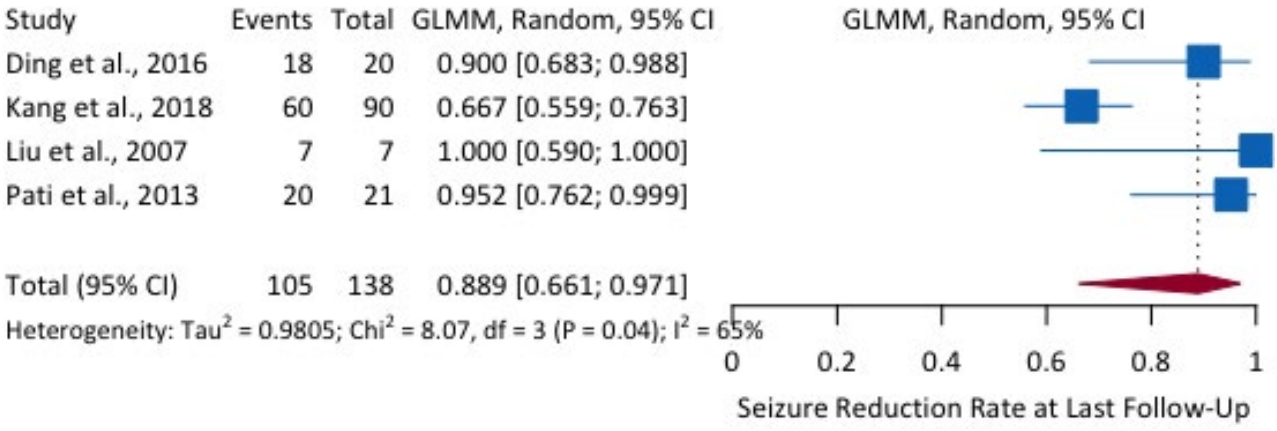

FIGURE 4 Forest plot of last follow-up seizure reduction rate with the most data for resective surgery studies. CI, confidence interval; GLMM, generalized linear mixed model

reduction in seizure frequency. One study assessing VNS + CC reported five of nine (55.6%, 95% CI = 23.1%–88.0%) patients with seizure reduction at last follow-up, and one DBS study reported 13 of 13 (100%) patients with seizure reduction at last follow-up. Two-proportion *z*-tests revealed significant differences in last follow-up seizure reduction between resective surgery + CC and VNS (88% vs. 48.1%, $p < .001$) and between DBS and VNS (100% vs. 48.1%, $p < .001$).

3.3 | Prognostic factors

For VNS, higher or longer duration of stimulation was associated with better outcomes in a few studies.[29,52] Atonic and tonic seizures were also reported to be better controlled than other seizure types.[54,60,63] Patients with intellectual disability, those with generalized tonic–clonic seizures, and those who required changes in AED regimen tended to have worse outcomes.[52–54] For CC, patients with a greater extent of callosotomy tended to have better seizure outcomes.[39,40,43,44] Absence of magnetic resonance imaging findings, preoperative brain damage, or presurgical lesions were also related to better outcomes.[39,47] CC was less effective for myoclonic seizures compared to other seizure types in one study.[38] Among resective surgery studies, shorter duration of preoperative epilepsy and hemispherectomy were associated with better seizure outcomes.[21,66] Adequate electrode placement was important for DBS success.[68]

3.4 | QOL, cognition, and behavior outcomes

3.4.1 | Vagus nerve stimulation

Eleven studies[29,36,53,54,56,58,59,61,63–65] commented on QOL, behavior, and/or cognition changes for LGS patients after treatment with VNS. Most patients were severely intellectually disabled at baseline[59,61,63–65] or had low mental age.[53] Common measures included parental or caregiver rating,[56,59,63] Weschler Intelligence Scale for Children,[53,61,65] and visual analogue scale.[56,61] Five studies[29,36,54,59,64] noted specific improvements in alertness for a majority of their LGS patients after VNS. Three studies generally noted QOL improvements after VNS,[36,56,63] whereas four studies[53,58,61,65] reported no significant changes or reductions in QOL, cognition, or behavior after VNS. Other findings included mild improvement in mental age[53]; a minority of patients exhibiting improvements in verbal communication, school work, memory, and mood[29]; and a minority of patients exhibiting improvements in adapting behavior/alertness.[65] For negative effects, one study reported a decline in mood for one patient of 24,[29] and another study reported behavioral problems in two patients of nine.[63] Of note, four studies[29,36,53,65] reported that observed changes in QOL, cognition, and behavior were all independent of seizure reduction outcomes.

3.4.2 | Corpus callosotomy

Eight studies[24,36,38–41,43,48] commented on QOL, behavior, and/or cognition changes for LGS patients after treatment with CC. Most patients were classified as mentally disabled or had a low intelligence quotient (IQ) at baseline.[24,36,38–41,43,48] Common measures included various forms of IQ testing[24,38,40,43] and neuropsychiatric evaluation.[39,41,43] Four studies[40,41,43,48] noted no deterioration or significant change in IQ or cognitive function in LGS patients after CC. Three studies reported improvements in attention span,[36] IQ (10/23 patients),[38] and cognitive function.[43] Two studies reported improvements in QOL, with one study finding the vast majority of 24 patients experiencing improvements[36] and another reporting 13 of 23 patients with QOL improvements.[38]

One study noted improvements in behavior in two of two patients.[39] Other findings included no behavior or attention changes,[48] 90% parental satisfaction after the procedure,[48] and a mixed CC/resective group showing IQ improvement.[24] Negative findings included IQ decline in two of 23 patients[38] and QOL decline in one of 23 patients.[38] Of note, three studies reported a strong correlation between attention/IQ improvements and seizure frequency reduction.[24,36,40]

3.4.3 | Resective surgery

Three studies[21,22,66] commented on QOL, behavior, and/or cognition changes for LGS patients after treatment with resective surgery. Patients had low IQ,[22] low social quotient,[21] or considerable behavioral issues at baseline.[66] Measures included IQ tests,[22] social quotient maturity scales,[21] and parental ratings.[66] One study[22] reported IQ improvements in 12 of 20 patients, memory improvements in eight of 20 patients, and QOL improvements in 13 of 20 patients. Another study[66] reported that 19 of 21 patients had improved behavioral functioning. There were also reports of no changes in IQ in three of 20 patients, no change in memory in 10 of 20 patients, and no change in QOL in four of 20 patients.[22] One study reported no significant difference in preoperative and postoperative social functioning.[21] Negative findings included decrease in IQ in five of 20 patients, decrease in memory in two of 20 patients, and decrease in QOL in three of 20 patients.[22] One study reported a correlation between better social functioning and seizure reduction.[21]

3.4.4 | Combination surgeries and DBS

One study[22] commented on QOL and cognition changes for LGS patients after treatment with combination resective + CC surgery. The study reported improvement in IQ for 17 of 23 patients, improvement in memory for eight of 23 patients, improvement in QOL for 18 of 23 patients, no change in IQ for six of 23 patients, no change in memory for 12 of 23 patients, no change in QOL for five of 23 patients, and decrease in memory for three of 23 patients. One study assessing DBS[68] reported eight of 13 patients becoming more independent, with a correlation between seizure reduction and increased independence.

Details of QOL evaluations by study can be seen in Table 1. See Table 2 for a summary of reported QOL/behavior/cognition changes by intervention and Table 3 for a detailing of these measures for studies reporting these outcomes.

3.5 | Complications

3.5.1 | Vagal nerve stimulation

Ten studies[28,29,54,56,58–61,63,65] commented on complications for LGS patients after treatment with VNS. All 10 studies reported that the majority of patients had no major complications, such as severe infections, vagal nerve lesions, or procedure-related complications. Voice alteration, hoarseness, and drooling/salivation were commonly reported, with 22 of 50 patients,[29] three of 13 patients,[58] 20 of 50 patients,[54] two of four patients,[56] and one of 10 patients[28] in various studies experiencing at least one of these adverse effects. Coughing was also noted in 15 of 20 patients in one study[29] and three of 13 patients in another study.[58] Of note, the aforementioned symptoms appeared to fade with decreased stimulation settings[28,29] or with time.[58] Other minor side effects included intractable headaches in one of three patients with increased stimulation,[60] incision site pain in five of 50 patients,[29] paresthesia in four of 50 patients,[29] mild infection in two of 50 patients,[29] increased tiredness in two of four patients,[56] agitation at high current in one of nine patients,[63] and dyspnea while sleeping in one of 10 patients.[28] More serious adverse events included surgical debridement and antibiotics for notable incisional infection in one of 13 patients,[58]

TABLE 2 Summary of reported QOL/behavior/cognition changes by intervention

Intervention	Positive/neutral effects	Negative effects
VNS	No reduction in QOL, cognition, or behavior; more alert; higher mental age; better verbal communication; better memory; better mood	Decline in mood; behavioral problems (rare)
CC	No reduction in IQ or attention span; improvements in IQ, cognition, and attention; improvements in QOL; improvements in behavior; parental satisfaction	IQ decline, QOL decline (rare)
Resective surgery	No difference in social functioning; no change in IQ, QOL, memory, and behavior	IQ, QOL, memory decrease (minority)

Abbreviations: CC, corpus callosotomy; IQ, intelligence quotient; QOL, quality of life; VNS, vagus nerve stimulation.

TABLE 3 Details of QOL/cognition/behavior outcomes for relevant studies

Authors	Mean/median age of patients, years	Interventions assessed	Domains tested	Measures	Baseline status	Outcome
Aldenkamp et al.	11.2	VNS	QOL, cognition	BDS, McCarthy scale, WISC, Dutch SRZ/SGZ/TVZ scale	Mental age 30.2 months; SRZ 3.6, SGZ 6.6, mood 7.3	After 24 months: mental age 34.4 months; SRZ 3.3, SGZ 7.3, mood 7.3
Cukiert et al.	8.6	VNS	QOL, attention	QOLIE-31, SNAP-IV questionnaires	N/A	Improvements in 85% for QOL and attention
Frost et al.	13	VNS	QOL	Unvalidated 5-point rating scale	N/A	After 3 and 6 months, ~60% showed improvement in alertness; mostly same for verbal, memory, school, mood, etc.
Hallböök et al.	10.75	VNS	QOL, cognition, behavior, mood	BSID, WPPSI-R, WISC-III, VAS, CBCL, Dodrill mood, Birleson depression	All but one IQ < 70	Most no changes in cognition, most improvement in QOL
Hornig et al.	10.2	VNS	Behavior	Parent Global Evaluation Score	All IQ < 70	Improvements in alertness, independence, learning
Hosain et al.	16.7	VNS	Behavior, cognition	N/A	N/A	No cognition, behavior side effects
Kostov et al.	13	VNS	Behavior	N/A	N/A	Improved alertness in 76.7% of patients
Nagarajan et al.	11.8	VNS	QOL, sleep, behavior	Parental rating	9 severely intellectually disabled, 4 moderately, 3 mildly	Most improved in behavior, alertness, awareness, language; sleep mostly unchanged
Lundgren et al.	9.5	VNS	QOL	Caregiver VAS	VAS score of 0	Most caregivers reported improvement, no worsening
Shahwan et al.	11.8	VNS	Behavior	Parental evaluation	Most severely intellectually disabled	Improved alertness and communication common
Zamponi et al.	13.84	VNS	QOL, behavior, cognition	Stanford-Binet, WISC-R, WAIS, VABS	All severely mentally disabled	No change in behavior, cognition; about half reporting better QOL
Chandra et al.	11.46	CC	Behavior, social quotient	VSMS, CBCL	IQ < 50 (mean 25.23); CBCL 69.25	No deterioration in behavior; IQ 26.43; CBCL 61.81
Turanli et al.	6.1	CC	Cognition	Neuropsychiatric and psychiatric evaluation	Mild to severe mental disability	No changes in IQ
Oguni et al.	N/A	CC	Cognition	Full-scale, performance, and verbal IQ	Most low intelligence	Small improvement in IQ w/ seizure improvement; small IQ decrease w/ no change in seizures
Lee et al.	7.6	CC	Cognition	WISC, WAIS, FSIQ, VIQ, PIQ, DQ	40.4 FSIQ	2 years: FSIQ 46.1; IQ increase of 8.6

(Continues)

TABLE 3 (Continued)

Authors	Mean/median age of patients, years	Interventions assessed	Domains tested	Measures	Baseline status	Outcome
Liang et al.	9.5	CC	QOL, cognition	WCIS-CR, QOLIE-31, FSIQ, VIQ, PIQ, IQ	FSIQ 56.09, VIQ 57.00, PIQ 56.17, QOL 44.78	Change: FSIQ 5.13, VIQ 3.26, PIQ 7.13, QOL 6.26
Provinciali et al.	16	CC	Behavior, cognition	Neuropsychiatric evaluation	IQ < 70	Improvements in posture and behavior
Tanriverdi et al.	N/A	CC	Cognition	Neuropsychiatric, FSIQ, PIQ, VIQ	Most mentally disabled (including non-LGS)	No difference in FSIQ, PIQ, VIQ (including non-LGS)
Ding et al.	9.70	Resective, resective + CC combo	QOL, cognition	IQ, MQ, QOL tests	Resection FSIQ: 58.05, combined surgery FSIQ: 56.96	67.4% improvement in FSIQ/MQ, 72.1% improvement in QOL
Kang et al.	9.3	Resective surgery	Behavior	Social maturity scale for SQ	Seizure-free SQ: 42.0; seizure-persistent SQ: 36.3	Last follow-up: seizure-free SQ 45.3; seizure-persistent SQ 22.3
Pati et al.	14	Resective surgery	Behavior	Parental rating	44% behavioral issues	Improvement in 88%

Abbreviations: BDS, deep brain stimulation; BSID, Bayley Scales of Infant Development; CBCL, Child Behavior Checklist; CC, corpus callosotomy; combo, combination; DQ, developmental quotient; FSIQ, full-scale IQ; IQ, intelligence quotient; LGS, Lennox–Gastaut syndrome; MQ, memory quotient; N/A, not available; PIQ, performance intelligence quotient; QOL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SGZ, Storend Gedragsschaal voor Zwakzinnigen – Maladaptive Behaviour Scale for the Mentally Retarded; SNAP-IV, Short Neuropsychological Assessment Proecdure - 4th version; SQ, social quotient; SRZ, Social Functioning Scale for the Mentally Retarded; TVZ, Temperamentsschaal voor Zwakzinnigen (assessment of temperament); VABS, Vineland Adaptive Behavior Scale; VAS, visual analogue scale; VIQ, verbal IQ; VNS, vagus nerve stimulation; VSMS, Vineland Social Maturity Scales; w/, with; WAIS, Wechsler Adult Intelligence Scale; WCIS-CR, Weschler Child Intelligenc Scale-Chinese Revision; WISC, Wechsler Intelligence Scale for Children; WISC-III, WISC-3rd Edition; WISC-R, WISC-Revised; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised.

premature current failure in two of four patients,[56] and aspiration adverse event in one of four patients.[56]

3.5.2 | Corpus callosotomy

Thirteen studies[24,28,35,36,38,39,40,42,44,45,47,48,49] commented on complications for LGS patients after treatment with CC. No surgical complications were seen in a subset of patients, with five of five patients,[42] 10 of 18 patients,[35] two of two patients,[47] four of eight patients,[44] and two of two patients[49] experiencing no complications. Similarly, no long-lasting mortality or morbidity was reported for any patients in five studies: five of five,[42] 16 of 16,[48] 24 of 24,[36] 14 of 14,[40] and 23 of 23.[38] A common side effect was disconnection syndrome, with one of 18 patients,[35] five of 16 patients,[48] 23 of 24 patients,[36] and one of eight patients[44] experiencing typical symptoms. Transient weakness was also noted in three of 18 patients,[35] two of eight patients,[44] and one of 14 patients.[28] Respiratory complications were noted in one of 18 patients[35] and one of two patients.[39] Aphasia was noticed in one of 23 patients[38] and one of 14 patients.[28] Other less common complications included mutism in two of 18 patients,[35] hyperammonemic encephalopathy in two of 16 patients,[48] urinary incontinence in two of 23 patients,[38] transient bradycardia in one of three patients,[45] subcutaneous abscess in one of 18 patients,[35] meningitis in one of 16 patients,[48] ataxia in one of 14 patients,[28] apraxia in one of 23 patients,[38] extension of ablation in one of three patients,[45] and subgaleal fluid collection in one of eight patients.[44]

3.5.3 | Resective surgery

Two studies[21,22] commented on complications for LGS patients after treatment with resective surgery. One study[22] reported no postoperative death or permanent complications in 20 of 20 patients, and another[21] reported minor bleeding in a few cases.

3.5.4 | Combination surgeries and DBS

One study assessing resective surgery + CC[22] reported no postoperative death or permanent complications in 23 of 23 patients. Another study[67] assessing VNS + CC reported no mortality related to the two procedures, but nine of nine patients experienced acute disconnection syndrome after CC. VNS-related hoarseness was also observed in two of nine patients and coughing in one of nine patients. One study assessing DBS[68] reported that two of 13 patients required explanation after initial implantation due to skin erosions.

See Table 4 for a summary of complications for palliative surgeries.

4 | DISCUSSION

Between the palliative interventions, our meta-analysis showed a significant difference between rate of seizure reduction at the last follow-up time point between VNS and CC (raw: 48.1% vs. 67.3%, random effects: 54.6% vs. 74.5%, $p < .001$). This difference persisted across each of the three postprocedure follow-up periods we analyzed. These results suggest that CC may be more likely to provide a lasting and worthwhile seizure reduction for LGS patients in comparison to VNS, similar to a finding in a previous meta-analysis.[30] Additionally, it should also be noted that, although other studies have reported the effects of VNS become more noticeable over time,[69,70] our meta-analysis did not find a difference in seizure reduction rate for VNS from the 0–6-month follow-up period to the 2+-year follow-up period. More long-term data for VNS in LGS patients will be needed to better assess this relationship.

Our meta-analysis found that resective surgery provided lasting and worthwhile seizure reduction for a large portion of LGS patients (raw: 76.1%, random-effects model: 88.9%). As expected, the rates of seizure reduction in resective surgery were higher than in the palliative surgery options. These results suggest that resective surgery should remain a first-line

TABLE 4 Summary of complications for palliative surgeries

Intervention	More common complications	Rarer complications
VNS	Voice alteration, drooling, hoarseness, coughing	Headaches, incision site pain, tiredness, mild infection, agitation, dyspnea, current failure, aspiration adverse event
CC	Disconnection syndrome, transient weakness	Respiratory complication, aphasia, mutism, encephalopathy, urinary incontinence, transient bradycardia, subcutaneous abscess, meningitis, ataxia, apraxia, extension of ablation, subgaleal fluid collection

Abbreviations: CC, corpus callosotomy; VNS, vagus nerve stimulation.

surgical option for LGS patients who present with identifiable or localized seizure foci on electroencephalogram. Unfortunately, many LGS patients present with more diffuse epileptiform discharges, diffuse injuries, and nonspecific imaging findings, but there has been some research suggesting favorable results for resective surgery even without localized seizure foci.[17–19] Of note, publication bias was detected for the group of four resective surgery studies, suggesting that the rate of seizure reduction for resective surgery patients in LGS may be inflated in the literature.

In looking at rates of seizure reduction among other less common surgeries, we found that a large portion of patients undergoing resective surgery + CC or DBS experienced lasting and worthwhile seizure reduction (88% and 100%, respectively). VNS + CC was less successful, with 55.6% of patients experiencing worthwhile seizure reduction. There appeared to be significant differences between resective surgery + CC versus VNS as well as between DBS and VNS. However, these less common surgeries assessed only a small number of patients, and CIs for rates of seizure reduction were relatively large. These results should not be interpreted as a suggestion advocating a resective + CC combination surgery over a traditional palliative approach. Future studies may be wise to investigate the potential differences in effectiveness of neuromodulation techniques such as DBS and VNS or better characterize the benefit of resective surgery + CC as an interaction between its component procedures (additive, synergistic, etc.).

In regard to QOL measures, a considerable portion of LGS patients undergoing VNS appeared to have improvements in alertness, and a few studies reported QOL improvements in general. Some studies reported no changes in any QOL measures after VNS. Improvements in cognition, memory, behavior, and mood appeared to be rarer, but negative effects on mood and behavior were also rare. In comparison, LGS patients undergoing CC reported some improvements in cognitive function and QOL, namely a few studies reporting improvements in IQ, attention, and ability to perform daily tasks due to notable seizure improvement. Reported improvements in behavior were rarer in CC. Similar to VNS, negative effects in CC were rare, with IQ and QOL decline seen in a few patients. Overall, the palliative procedures appear to have comparable rates of QOL improvement or lack of deterioration, with negative QOL effects being rare in both procedures. However, QOL, cognition, and behavior changes appeared to be tied to seizure reduction for CC patients but independent of seizure reduction in VNS patients. Thus, although VNS appears to have lower rates of successful seizure reduction in comparison to CC, it may not necessarily be the case that VNS provides less QOL or cognition improvement. VNS patients appear to have notable improvements in traits such as alertness, which may be more important for some caregivers and parents.[29] Providers may take these data into account when considering palliative surgery options.

Of note, resective surgery and resective + CC surgery showed considerable rates of improvement in IQ, memory, and QOL, with only a small minority of patients experiencing deterioration in these measures. These results suggest that the seizure reduction rates in resective surgery techniques appear to have a direct correlate with improvements in QOL and cognition. Again, more data will be needed to better assess these techniques.

Our study's findings on complications were concordant with clinical observations, with CC having higher rates of adverse events, both major and minor, when compared to VNS or DBS. A notable issue for some CC patients is disconnection syndrome, which comprises a complex and often varying set of symptoms.[71] The risk of disconnection syndrome must be weighed with likelihood of seizure reduction, as it appears both may be increased with more complete or total corpus callosotomy.[72] Other, more serious, complications such as encephalopathy, ataxia, and respiratory complications were reported to occur after CC in a few patients; in general, the risk is low. Complications for VNS include voice alteration, hoarseness, drooling, salivation, and coughing commonly being reported. However, many of these complications were tied to the level of stimulation being used and were managed accordingly. Severe infections and respiratory complications were seen in a small minority of VNS patients.

Our study had numerous limitations. To increase power, we did not control for seizure type when conducting analyses. Additionally, we were not able to aggregate quantitative data on QOL, behavior, or cognition outcomes, as there was significant heterogeneity in how these outcomes were defined and measured across studies. As noted by the documentation of tests in Table 3, there remains no consensus on how to measure these outcomes in the presence of severe impairments such as typically seen in LGS. Current research endeavors by psychologists and psychometricians are adapting population-standardized measures and developing new measures that are commensurate with the range of abilities and sensitive to meaningful change in severely impaired patients, but specific recommendations are still forthcoming.[73] This is a significant limitation, as QOL improvements have been noted to be a more important outcome measure compared to seizure reduction for some caregivers.[29] In regard to seizure reduction rate, we were unable to compare outcomes for different etiologies or different types of CC (e.g., partial versus complete) due to lack of data or lack of consistent delineation of these categories within studies. Also, a network analysis was not possible due to study heterogeneity within interventions, a lack of trials, and uncertain transitivity. Our study also had numerous strengths, with a quantitative evaluation of seizure reduction for various surgical interventions in a

large number of LGS patients, an analysis of the temporal trends in seizure reduction within and between interventions, and a documentation and aggregation of numerous QOL measures and complications for different interventions.

5 | CONCLUSION

Resective surgery continues to show remarkable seizure reduction rate and QOL improvements for LGS patients with localized seizure foci, and it has proven to be the standard of care for any patient with identifiable epileptogenic zone, including those with LGS. CC may be a better palliative measure than VNS in regard to seizure reduction rate, but providers and caregivers should consider that VNS may provide a similar or higher level of QOL improvement with lower risk of procedure-related adverse events. Resective surgery + CC and DBS also show promise for a small subset of LGS patients.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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