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CRITICAL REVIEW

Not all that glitters is gold: A guide to surgical trials in epilepsy

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SUMMARY

Epilepsy surgery is often the only effective treatment in appropriately selected patients with drug-resistant epilepsy, a disease affecting about 30% of those with epilepsy. We review the evidence supporting the use of epilepsy surgery, with a focus on randomized controlled trials (RCTs). Second, we identify gaps in knowledge about the benefits of epilepsy surgery for certain populations, the challenges of individualizing the choice of surgery, and our lack of understanding of the mechanisms of surgical outcomes. We conducted a search (MEDLINE, Embase, Cochrane, Clinicaltrials.gov) on March 2, 2016, to identify epilepsy surgery RCTs, systematic reviews, or health technology assessments (HTAs). Abstracts were screened to identify resective, palliative (e.g., corpus callosotomy, multiple subpial transection [MST]), ablative (e.g., Laser interstitial thermal therapy [LITT], gamma knife radiosurgery [RS]), and neuromodulation (e.g., cerebellar stimulation [CS], hippocampal stimulation [HS], repetitive transcranial magnetic stimulation [rTMS], responsive neurostimulation [RNS], thalamic stimulation [TS], trigeminal nerve stimulation [TNS], and vagal nerve stimulation [VNS]) RCTs. Study characteristics and outcomes were extracted. Knowledge gaps were identified. Of 1,205 abstracts, 20 RCTs were identified (resective surgery including corpus callosotomy [n = 7], MST [n = 0], RS [n = 1, 3 papers], LITT [n = 0], CS [n = 1], HS [n = 2], RNS [n = 1], rTMS [n = 1], TNS [n = 1], TS [n = 1], and VNS [n = 5]). Most studies targeted patients with temporal lobe epilepsy (TLE) and none examined the effectiveness of resective surgical therapies in patients with extra-TLE (ETLE) or with specific lesions aside from mesial temporal lobe sclerosis. No pediatric surgical RCTs were identified except for VNS. Few RCTs address the effectiveness of surgery in epilepsy and most are of limited generalizability. Future studies are needed to compare the effectiveness of different surgical strategies, better understand the mechanisms of surgical outcomes, and define the ideal surgical approaches, particularly for patients with high or very low cognitive function, normal imaging, or ETLE.

KEY WORDS: **Evidence-based medicine, Epilepsy surgery, Neuromodulation, Laser interstitial thermal therapy, Gamma knife surgery, Clinical trial, Outcomes.**

Drug-resistant epilepsy (DRE) is a fatal disease with 1% of patients succumbing to sudden unexpected death in epilepsy (SUDEP) each year unless seizure freedom is attained.[1,2] It is imperative to identify and refine effective therapies. Resective epilepsy surgery, in appropriately selected patients, is the accepted treatment of choice for DRE as supported by two randomized clinical trials,[3,4] multiple retrospective cohort series, and a practice parameter issued by the American Academy of Neurology recommending a surgical evaluation for any patient with uncontrolled disabling complex partial seizures.[5] Similarly, a plethora of nonresective yet surgical DRE treatments have flourished recently, including various neuromodulation procedures[6–18] and thermal-based[19] and radiation-based

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Key Points

- Twenty epilepsy surgery RCTs were identified, including 7 resective (±palliative), 1 ablative, and 12 neuromodulation trials
- Mesial temporal lobe epilepsy (TLE) was the surgical target in most studies; no studies examined the effectiveness of surgery for extra-TLE (ETLE)
- Future studies are needed to test the effectiveness of various surgical strategies and to better understand surgical outcome mechanisms
- The ideal surgical approaches for those with high but also those with very low cognitive function, normal imaging, or ETLE remain to be determined

neurosurgeries.[20] A position statement by the Practice Management Committee Health Care Reform Workgroup of the American Epilepsy Society called for access and insurance coverage for all patients with epilepsy for more aggressive therapeutic strategies, including neurosurgery and implanted electronic devices, when medications fail to yield optimal seizure control.[21] As new surgical therapies become available, it is essential to realize that not all "epilepsy surgery" is created equal because the evidence, risks, costs, and outcomes vary among the different procedures.

In this critical review, we analyze the evidence supporting each type of epilepsy surgery treatment, focusing on randomized controlled trial (RCT) data. We review short-term risks and benefits and highlight the known long-term outcomes. Such a comprehensive analysis allows us to identify knowledge gaps in the field of epilepsy surgery, particularly in relation to adequately individualizing the choice of surgery and understanding the mechanisms determining epilepsy surgery outcomes. This endeavor is particularly timely because our surgical patient population is becoming more complex, with a growing proportion of resective epilepsy surgeries being performed now for patients with DRE and normal brain imaging, and an even faster expanding population undergoing complex procedures with invasive EEG recordings without a resulting resection.[22]

Methods

We conducted a search of MEDLINE, Embase, Cochrane, and Clinicaltrials.gov on March 2, 2016 (see Appendix S1 for search strategy), to identify epilepsy surgery RCTs (resective or nonresective, original studies, systematic reviews, or health technology assessments [HTAs]) without publication date restriction. Abstracts were screened by both study coauthors to identify resective, palliative (e.g., corpus callosotomy, multiple subpial transection [MST]), ablative (e.g., laser interstitial thermal therapy [LITT], gamma knife radiosurgery [RS]), and neuromodulation (e.g., cerebellar stimulation [CS], hippocampal stimulation [HS], responsive neurostimulation [RNS], repetitive transcranial magnetic stimulation [rTMS], thalamic stimulation [TS], trigeminal nerve stimulation [TNS], vagal nerve stimulation [VNS]) RCTs. Study characteristics, target population, outcomes, strengths, and limitations were extracted. Knowledge gaps in the area of epilepsy surgery and future directions are discussed.

The Evidence for Resective Surgery

Summary of available trials

Seven resective surgery RCTs for epilepsy, most single-center studies in high-resource countries, were identified (Table 1).[3,4,23–27] Every RCT was carried out in adults with drug-resistant temporal lobe epilepsy (TLE), though a few also targeted teenagers[3,4,26,27] and children,[26] according to their eligibility criteria, in addition to adults. Follow-up ranged from 6 months to 2 years. Two RCTs compared the safety and efficacy of medical versus surgical treatment in patients with TLE. These include the RCT by Wiebe et al.[3] the most highly cited epilepsy surgery RCT, and, most recently, the ERSET (Early Randomized Surgical Epilepsy Trial) study by Engel et al.[4] in patients with new-onset drug-resistant epilepsy (within 2 years of becoming drug-resistant). Four RCTs compared small to larger surgical resections, including temporal lobectomy with or without sparing of the superior temporal gyrus,[23] 2.5- versus 3.5-cm temporal resection,[24] temporal lobectomy with partial versus complete hippocampectomy,[25] and temporal lobectomy with or without anterior corpus callosotomy in patients with developmental delay only.[26] Finally, one RCT compared two surgical approaches for selective amygdalohippocampectomy (SAH), that is, the transsylvian versus the transcortical approach.[27]

Benefits and risks of resective epilepsy surgery

Medical versus surgical therapy

Seizure outcome was the primary outcome in most studies. In patients with early-onset drug-resistant epilepsy (ERSET study), 73.3% (11/15) of those in the surgical group were free of disabling seizures at 2 years compared to no one (0/23) in the medical arm.[4] Quality-of-life (QOLIE-89) scores improved to a greater extent in the surgical compared to the medical group but did not reach statistical significance. Days per month socializing and proportion of those driving at 24 months were significantly higher in the surgical compared to the medical group. One patient had transient neurological deficits in the surgical group (stroke), and three patients in the medical group experienced status epilepticus. In the Wiebe et al.[3] study, 58% of those in the surgical group (64% excluding those who did not have

Table 1. Summary of randomized controlled trials of resective and ablative epilepsy surgery

Intervention	Population[a]	Study setting	Follow-up	Outcomes
Temporal lobectomy vs. medical management[4]	• Drug-resistant TLE for ≤2 years (age ≥12) • n = 23 medical, n = 15 surgical • Mean age: 30.9 ± 10.1 (medical) vs. 37.5 ± 11.1 (surgical) • Female 39.1% (medical) vs. 73.3% (surgical) • Mean duration: 5.3± (2.8–13.4) (medical) vs. 5.2± (3.2–15.8) (surgical)	Multicenter, tertiary care	2 years	Primary • Freedom from disabling seizures—number of seizure-free patients at 2 years: 11/15 (surgical) vs. 0/23 (medical) (odds ratio ∝; 95% CI, 11.8–∝; p < .001) Secondary • QOL (QOLIE-89) mean improvement 12.6 (surgical) vs. 4.0 (medical), but not statistically significant • Driving at 24 months 80% (surgical) vs. 22% (medical) (p < .001) • Days/month socializing with friends 6.5 days (surgical) vs. −1 day (medical) (p = .002) • Employment status, sick days, socializing with family not statistically different between groups Complications: • 1 transient neuro deficit (stroke) (surgical) vs. 3 status epilepticus episodes (medical)
Temporal lobectomy vs. medical management[3]	• Drug-resistant TLE (age ≥16) • n = 40 medical, n = 40 surgical • Mean age: 34.4 ± 9.9 (medical) vs. 35.5 ± 9.4 (surgical) • Female 47.5% (medical) vs. 57.3% (surgical) • Mean duration: 18.2 (medical) vs. 21.2 (surgical)	Single-center, tertiary care	1 year	Primary • Freedom from seizures that impair awareness—proportion seizure free at 1 year: 58% (surgical; 64% excluding those who did not undergo surgery) vs. 8% (medical) (p < .001) Secondary • Free of all seizures: 38% (surgical; 42% excluding those who did not undergo surgery) vs. 3% (medical) (p < .001) • QOL (QOLIE-89): 73.8 (surgical) vs. 64.3 (medical) (p < .001) • Employed or attending school: 56.4% (surgical) vs. 38.5% (medical) (p = .1) Complications: • One death (medical); no deaths (surgical) but 10% had neurological complications (surgical) vs. 0% (medical)
Temporal lobectomy ± sparing of superior temporal gyrus[23]	• Drug-resistant TLE • n = 16 STG resected, n = 14 STG preserved • Mean age: 31.9 (7.5) (resected) vs. 33.6 (11.1) (preserved) • Females 50% in each group • Mean duration: 19.9 (resected) vs. 23.3 (preserved)	Single-center, tertiary care	6–8 months	• Free of any seizures: 60% (resected) vs. 55% (preserved) Complications: • Confrontation naming: Boston Naming Test and Visual Naming: no differences; older age predicted language dysfunction
Temporal lobectomy 2.5-cm vs. 3.5-cm resection[24]	• Drug-resistant TLE (age >18) • n = 104 (2.5 cm) vs. n = 103 (3.5 cm) • Mean age: 39.5 ± 13.9 (2.5 cm) vs. 39.8 ± 12.5 (3.5 cm)	Multicenter, tertiary care	1 year	• Seizure outcome (Engel class I): 74% (2.5 cm) vs. 72.8% (3.5 cm) (p = .843) • One death (2.5 cm) suicide; one death (3.5 cm) accidental death Complications: • No statistical differences between groups in regard to neurological complication, visual

Continued

Table 1. Continued.

Intervention	Population[a]	Study setting	Follow-up	Outcomes
	• Females 49% (2.5 cm) vs. 54.4% (3.5 cm) • Mean duration: 22.5 ± 14 (2.5 cm) vs. 21 ± 14.3 (3.5 cm)			field defects, or surgical complications (overall below 3% neurological complications and 1.67% permanent morbidity)
Temporal lobectomy ± partial vs. complete hippocampectomy[25]	• Drug-resistant TLE (>18 but <40) • n = 34 (partial) vs. n = 36 (complete) • Mean age: 30.5 (partial) vs. 31.2 (complete) • Females 50% (partial) vs. 55.6% (complete) • Mean duration: 19.2 (partial) vs. 21.4 (complete)	Single-center, tertiary care	1 year	• Seizure freedom: 69% (complete) vs. 38% (partial hippocampal resection) (p = .009) • No cognitive effects (visual or verbal memory) depending on extent of resection Complications: • 7% minor complications: n = 2 (partial) vs. n = 3 (complete)
Temporal lobectomy ± anterior corpus callosotomy[26]	• Drug-resistant TLE and developmental delay (age 6–40) • n = 30 ATL, n = 30 ATLcc • Mean age: 16.97 ± 6.91 (ATL) vs. 16.33 ± 6.85 (ATLcc) • Females 33.3% (ATL) vs. 53.3% (ATLcc) • Mean duration: 13.57 (ATL) vs. 13.19 (ATLcc)	Single-center, tertiary care	2 years	• Engel class I: 73.3% (ATLcc) vs. 60% (ATL) • Full-scale IQ improved: 63.6% (ATLcc) vs. 56.7% (ATL) • QOL improved: 73.7% (ATLcc) vs. 33.3% (ATL) Complications: • No permanent complications in either group • ATLcc: 2 urinary incontinence, 1 aphasia, 2 apraxia • ATL: 2 aphasia, 2 apraxia
SAH with transsylvian vs. transcortical approach[27]	• Drug resistant TLE (≥16) • n = 41 transsylvian (TS) vs. n = 39 transcortical (TC) • Mean age: 36.76 (9.72) • Females 51.2% (TS) vs. 51.3% (TC) • Mean duration: not provided by TS vs. TC but >20 in all groups	Single center, tertiary care	~7.3 months (avg) postsurgery	• 76.9% of TC vs. 73.2% of TS patients were seizure free (p = .80) • Fluency improved in 29.7% of TC group but in only 5% of TS group with gains significant in TC group (p < .001) but not in TS group (p = .642) Complications: • Not provided
Low-dose (20 Gy) vs. high-dose (24 Gy) gamma knife radiosurgery[20,39,40]	• Drug-resistant TLE with unilateral hippocampal sclerosis (adults) • n = 13 (high) vs. n = 17 (low) • Mean age: 34.1 (7.9) • Females 60% overall • Mean duration: n/a	Multicenter, tertiary care	3 years	• Seizure freedom (3 years): 76.9% (high) vs. 58.8% (low) • Neuropsychological testing (2 years; n = 26 patients) not different from baseline • QOL (QOLIE-10) (3 years): improvement in year 1 maintained in years 2–3 (low) vs. improvements in years 1 and 2 then sustained in year 3 (high) Complications: • No differences in adverse events, including headaches, use of steroids, visual field defects (n = 24 available for VFDs at 2 years) by dose; however, 1 patient had serious edema in high-dose group requiring temporal lobectomy

ATL, anterior temporal lobectomy; ATLcc, anterior temporal lobectomy with corpus callosotomy; QOL, quality of life; STG, superior temporal gyrus; TC, transcortical; TLE, temporal lobe epilepsy; TS, transsylvian; VFD, visual field defect.

[a]Ages or durations are in years unless otherwise specified.

surgery) and 8% of those in the medical group were free of seizures impairing awareness at 1 year (those free of all seizures were 42% excluding those who did not have surgery vs. 3% in the medical arm). QOL and employment or school attendance was significantly higher in the surgical compared to the medical group. One patient died in the medical group, and 10% of patients in the surgical group experienced adverse events from surgery.

Extent of surgical resection

The study by Hermann et al.[23] comparing temporal lobectomy with and without sparing of the superior temporal gyrus found no difference between the groups with respect to seizure outcomes (60% resected vs. 55% preserved) or confrontation naming. The study by Schramm et al. comparing temporal lobectomy with a minimum resection length of 2.5 versus 3.5 cm for the hippocampus and parahippocampal gyrus also found no significant difference in surgical outcomes in regard to Engel Class I seizure outcome (74% for 2.5 cm vs. 72.8% for 3.5 cm group), mortality, neurological complications, visual field defects, or surgical complications. The study by Wyler et al.[25] comparing temporal lobectomy with partial (to anterior edge of cerebral peduncle) or complete (to level of superior colliculus) hippocampectomy reported a significantly higher proportion of patients who were seizure free in the complete versus the partial resection (69% vs. 38%). There were no differences in cognitive outcomes or complications between the two groups. The study by Liang et al.[26] comparing temporal lobectomy with or without corpus callosotomy in patients with developmental delay reported no statistical difference between the groups with respect to seizure outcome (Engel Class I 73.3% with corpus callosotomy vs. 60% without) or full-scale IQ improvement. However, QOL was significantly improved in 73.3% of those with corpus callosotomy compared to 33.3% in those without. Finally, the study by Lutz et al.[27] did not find any difference in seizure freedom in those who underwent transcortical versus transsylvian SAH (76.9% vs. 73.2%, respectively), but fluency improvements and gains were significantly higher in the transcortical than in the transsylvian group.

Limitations of current resective epilepsy surgery RCTs

RCTs are the ultimate study design to compare the effectiveness of two interventions because they generally minimize bias and confounding. However, epilepsy surgical RCTs are ethically challenging, resulting in limitations even with the most carefully designed studies. For example, it would have been unethical to blind patients to their interventions in the ERSET and Wiebe et al. studies comparing medical to surgical therapy.[3,4] As a result, bias exists (see Table 2) because the outcomes of interest, that is, seizures and QOL, are reported by patients who are not blinded to the intervention they received.[3,4] A recent Cochrane review assessed bias of several existing epilepsy resective RCTs, as we did for the RCTs identified in this review (see Table 2).[28] For example, some studies were described as randomized, but no details were provided regarding the generation of the random list.[3,25] Other studies do not provide information on allocation concealment.[25,26] Other challenges include the significant heterogeneity that exists among patients in regard to age of onset, epilepsy duration, and epilepsy etiology.[29] The five resective epilepsy surgery RCTs also have limited generalizability because they include only patients with TLE, often mesial TLE only, as in the Schramm et al. and the ERSET studies.[4,24] In addition, recruitment processes and the lengthy baseline testing for the ERSET study resulted in slow patient accrual, with only 38 of the planned 200 patients recruited, precluding meaningful conclusions about certain outcomes (e.g., neuropsychological outcomes).[30] However, the ERSET trial still provides key information that can inform future epilepsy surgery trials.[30] When it comes to the RCTs comparing smaller versus larger resections, the biggest limitation is usually the lack of pre- and post-MRI volumetric studies and smaller sample sizes precluding adequate outcomes analyses or analyses by subgroup. Finally, another important limitation of resective RCTs is the lack of data on long-term outcomes. This is particularly important because so many patients who undergo epilepsy surgery are young and must understand what their outcomes will be decades ahead.

The evidence for neuromodulation

Summary of available trials

Twelve RCTs for neuromodulation in epilepsy were identified (Table 2). Most (9/12) were multicenter studies.[3,9,11,12,14,18,31–33] One was specifically a pediatric RCT.[17] All were carried out in patients with drug-resistant epilepsy, although the extent of epilepsy characterization was variable across studies: two studies evaluated patients with drug-resistant mesial TLE,[12,34] five specified "partial" or "focal" epilepsy in their study criteria,[11,14,18,32,33] one targeted adults with malformations of cortical development,[13] and the rest required only "medically refractory seizures," including two that explicitly included patients with generalized epilepsy.[6,17] Several RCTs (5/12) evaluated VNS (whether implanted[9,14,17,31,32] or transcutaneous[6]). Two evaluated HS (implanted[34] or transcranial[12]), and the rest individually evaluated CS,[35] TNS,[11] rTMS,[13] thalamic stimulation,[33] and RNS.[10,16,18] All pivotal RCTs were followed by open-label extensions that allowed long-term data collection.[7,8,10,16,36]

Benefits and risks of neuromodulation

Seizure control and complications

Different measures of seizure frequency were used to demonstrate the safety and efficacy of different

Table 2. Risk of bias assessment of resective and ablative randomized controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel, and outcome assessment (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Temporal lobectomy vs. medical management						
Engel et al. (2012)[4]	Low	Low	Moderate	Low	Low	Low
Wiebe et al. (2001)[3]	Unclear	Low	Moderate	Low	Low	Low
Temporal lobectomy with and without sparing of superior temporal gyrus						
Hermann et al. (1999)[23]	Unclear	Unclear	Moderate	Low	Low	Low
Temporal lobectomy 2.5- vs. 3.5-cm resection						
Schramm et al. (2011)[24]	Low	Low	Low	Low	Low	Low
Temporal lobectomy with partial vs. complete hippocampectomy						
Wyler et al. (1995)[25]	Unclear	Unclear	Low	Low	Low	Low
Temporal lobectomy with and without anterior corpus callosotomy						
Liang et al. (2010)[26]	High	Unclear	Unclear	Low	Low	Low
Selective amygdalohippocampectomy with transsylvian vs. transcortical approach						
Lutz et al. (2004)[27]	Unclear	Unclear	High	Low	Low	Low
[a]Gamma knife radiosurgery low vs. high dose						
Barbaro et al. (2009)[20]	Low	Unclear	Unclear	Low	Low	Low

[a]Follow- up analyses of the Barbaro[20] studies include Hensley-Judge et al.[39] and Quigg et al.[40]

neuromodulation modalities (Table 3), including rate of reduction in monthly seizure frequency between treatment and control study arms, seizure reduction from preintervention to end of study in either treatment or control arm, responder rates as defined by proportion of patients with >50% reduction in seizure frequency, and complete seizure freedom. Overall, the blinded phases of the two VNS pivotal RCTs showed that seizure frequency decreased by more than 50% in 23–31% of individuals in the treatment groups compared with 13–15% in the placebo groups.[9,14,31] These trials led to the U.S. Food and Drug Administration approving in 1997 the use of VNS as adjunctive therapy in individuals older than 12 years with partial epilepsy refractory to medical treatment. Since then, open-label extensions of these trials and multiple observational studies have reported further reductions in seizure frequency fueling support for the use of this device.[7,8,36] However, the one available pediatric RCT[17] did not show a seizure control benefit to VNS (responder rate of 16% in high- vs. 21% in low-output stimulation), and the one prospective RCT comparing VNS to medical therapy, rather than comparing high to low settings of stimulation as done previously, did not show any difference in seizure frequency or responder rates between the treatment and control arms.[32] Complications of VNS placement included hoarseness (30%), dyspnea (13%), and infection (12%).[14,31] An attempt to minimize the implantation side effects led to a recent pilot RCT in adults evaluating transcutaneous stimulation of the somatic sensory territory of the vagus nerve at the Ramsay-Hunt zone between the external auditory canal and the conchal cavity, with promising results.[6] A similar pediatric study of transcutaneous VNS is ongoing.[15]

Responsive neurostimulation (RNS) is the only other FDA-approved neuromodulation treatment. Its benefits are similar to the VNS results reported earlier, with a 37.9% reduction in seizure frequency in the treatment arm versus 17.3% reduction in the sham group at the end of the blinded phase.[18] No difference in responder rates was seen between the treatment and sham groups during the blinded phase of the study; additional reductions in seizure frequency to 44% at 1 year and 53% at 2 years were reported during the open-label extension.[10,16] Complications of RNS included a 4.7% rate of intracerebral hemorrhage and a 9% rate of infection after a mean of 5.4 years of follow-up, requiring neurostimulator explantation in 4.7% of the cases.[10,16]

Additional non-FDA-approved neuromodulation methods showing similar results to the VNS and RNS are found in Table 3.

Quality of life and functional outcomes

PuLsE (Open Prospective Randomized Long-term Effectiveness Trial) demonstrated improvements in QOL related to VNS (Table 2), although no differences were seen in measures of depression, adverse event profiles, and antiepileptic drug (AED) load between groups.[32] Mood follow-up of children in the Klinkenberg et al.[37] study showed improvements in mood, epilepsy restriction, and psychosocial adjustment in baseline to open-label measures.

Conversely, all patients in Aihua et al.[6] showed improved mood and QOL profiles.

Trigeminal nerve stimulation was correlated with improvement in depression within and between groups (baseline to end of study and stimulated to sham).[11]

Table 3. Summary of randomized controlled trials of neuromodulation

Intervention	Population	Study setting	Follow-up	Outcomes
Vagus nerve stimulation				
High vs. low treatment paradigm[9,31]	• Refractory seizures (unclear how epilepsy type was ascertained) • n = 54 (high) vs. n = 60 (low) • Mean age 33.1 years (high) vs. 33.5 years (low) • Females 39% (high) vs. 37% (low) • Mean duration 23.1 years (high) vs. 20 years (low)	Multicenter	12 weeks after 2-week recovery from implantation	• 24.5% reduction in seizure frequency in high vs. 6.1% for the low (p = .01) • At least 50% reduction in SF in 31% of high vs. 13% of low (p = .02) • No patients became seizure free • No difference in results by seizure types Complications: • Hoarseness • One death due to myocardial infarction, and one patient with vocal cord paralysis
High vs. low treatment paradigm[14]	• Refractory partial-onset seizures with alteration of consciousness • n = 95 (high) vs. n = 103 (low) • Mean age 32.1 years (high) vs. 34.2 years (low) • Females 48% (high) vs. 57% (low) • Mean duration 22.1 years (high) vs. 23.7 years (low)	Multicenter	12–16 weeks after 2-week ramp-up period	• Primary: 27.9% reduction in seizure freq relative to baseline in high vs. 15.2% reduction in low (p = .04). • No difference in between-group comparison for 50% responders (15.7% responder rate in low vs. 23.4% RR in high) • One patient (high) seizure free • Perceived improvement in well-being in all groups (high and low vs. baseline) Complications: • Hoarseness (30%) • Dyspnea (13%) • Infection (12%)
VNS in children:[17] High vs. low output for 20 weeks, then all got high for 19 weeks	• 41 children total (35 with focal epilepsy and 6 with generalized epilepsy) • N = 21 in high; 20 in low • Mean age 10 years 11 months (high) and 11 years 6 months (low) • Mean duration 7 years 8 months (high) vs. 9 years 5 months (low)	Single-center	20 weeks	At end of RCT phase: • 50% reduction in SF in 16% of high and 21% of low At end of open label: • 26% had 50% reduction Complications: • Voice alterations (20%) • Coughing (7%) • Throat pain (7%) • Infection (5%)
Transcutaneous VNS:[6] Ramsay-Hunt zone stimulation (tx grp) vs. earlobe (control) stimulation	• 60 divided into • children[a] + adults • Mean age 34.5 years (26.5–41.3) in tx group and 29.0 (24.5–42) in control • Mean duration 10.7 years in tx and 17.6 in control • Seizures types: SPS (65%), CPS (11%), Gen (23%) in tx vs. 71%,14%, and 14%, respectively, in control	Single-center	12 months	• Monthly seizure frequency 4.0 (tx) vs. 8.0 (control) (p = .003) • All patients showed improved SAS, SDS, LSSS, QOLIE-31 scores Complications: • Dizziness (3%) • Drowsiness (9%)

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Table 3. Continued.

Intervention	Population	Study setting	Follow-up	Outcomes
PuLsE (Open Prospective Randomized Long-term Effectiveness):[32] VNS + BMP (best medical practice) vs. BMP	• Adults with pharmacoresistant focal seizures (48 with VNS + BMP, and 48 with BMP alone) • Mean age: 38 years in tx vs. 41 years in control • 50% female in tx vs. 44% in control • Mean duration: 25 years in tx vs. 25 years in control	Multicenter—terminated early owing to low enrollment	24 months in seven patients, 12 months in 60	• Primary endpoint: Mean change from baseline HRQoL (QOLIE-89): improvement of 5.5 points in VNS + BMP vs. 1.2 in BMP alone • No difference in secondary endpoints: ○ Seizure frequency ○ Responder rate, ○ CES-D ○ NDDI-e ○ AEP ○ AED load Complications: • Transient vocal cord paralysis (4%) • Brief respiratory arrest (3%)
Trigeminal nerve stimulation tx eTNS 120 Hz vs. control eTNS 2 Hz[11]	• 50 patients with at least 2 partial-onset seizures/month (25 in tx arm and 25 in control arm): • Mean age 33.1 years in tx vs. 34 in control • 64% female in tx vs. 44% in control • Mean duration 16.7 years in tx vs. 12.0 in control	Multicenter	18 weeks	• No difference in responder rate between tx group (31%) and control group (21.1%) • Seizure frequency as measured by response ratio improved within each group compared to baseline, but no difference among tx and control • Improvement in depression (BDI score change of −8.13 in tx and −3.95 in ctrl; p = .002) within and between groups Complications: • Skin irritation (14%) • Anxiety (4%) • Headache (4%)
Thalamic stimulation[33]	• Adults with refractory partial seizures • 110 participants: 54 stimulated and 55 control • Mean age 35.2 years in tx vs. 36.8 years in control • Female 54% in tx vs. 46% in ctrl • Mean duration: 21.6 years in tx vs. 22.9 years in control	Multicenter	3 months blinded followed by 9 months open label with all on	• 29% greater reduction in seizures in last month of blinded phase in tx vs. control, as estimated by generalized estimating equations model • By 2 years: responder rate 54% • 14 patients were seizure free for at least 6 months Complications: • Paresthesias (18%) • Implant site pain (11%) • Infection (9%) • Need to replace leads (8%) • Overall, 16% withdrew because of side effects
Responsive neurostimulation[10,16,18]	• Adults with refractory partial epilepsy: 97 active stimulation vs. 94 with sham stimulation • Mean age: 34.0 in tx vs. 35.9 in sham • Female: 48% in tx vs. 47% in control	Multicenter	12-week blinded period followed by 84-week open-label period	• Mean % change in seizure frequency the blinded period was −37.9% in tx arm vs. −17.3% in sham (p = .012) • Responder rate 29% in tx grp vs. 27% in sham • 2 subjects in tx were seizure free for the blinded phase

Continued

Table 3. Continued.

Intervention	Population	Study setting	Follow-up	Outcomes
	• Mean duration: 20.0 years in tx vs. 21.0 years in sham			• QOLIE-89 scores improved in tx and sham, continued through 1 and 2 years Complications: • Serious adverse event rate of 12%; 4.7% rate of intracerebral hemorrhage; infection 5.2% at end of open-label phase, and 9.0% after mean 5.4 years of follow up requiring neurostimulator explantation (4.7%) Open label: • Median % reduction in seizure frequency of 44% at 1 year and 53% at 2 years • Statistically significant improvement in QOLIE scales at 1 and 2 years
Repetitive transcranial magnetic stimulation (rTMS)[13]	• Adults with MCD • 12 patients with rTMS (1 Hz, 1,200 pulses) vs. 9 patients with sham rTMS • Age: mean 21.3 (6.4) in tx vs. 22.7 (10.3) sham	Single-center	60 days	• 58% reduction in seizure frequency by week 8 in active arm vs. no difference from baseline in sham • Improvement in subjective measures of social interaction and energy level and cognition in tx arm Complications: • 25% in tx and 22% in sham headache; no worsening of seizures; one patient in sham (11%) had insomnia
Hippocampal stimulation Unilateral or bilateral hippocampal stimulation through 4-contact electrode implanted along the hippocampus, and 135-Hz continuous cathodal stim of all electrodes involved in seizure generation (tx) vs. hippocampal implantation without stimulation (ctrl)[34]	• Drug-resistant MTLE • 2 patients with tx and 4 pts in control • Mean age 30 years in tx vs. 35–46 in ctrl • Baseline seizure frequency: 10 sz/month median in control and 12 in tx	Multicenter	7 months	• None statistically significant: • Mean seizure reduction of 45% in tx vs. 60% increase in ctrl. • ½ patients in tx group had a >50% reduction Nonsignificant trend • Improvement with HS in the frequency of all seizures (but not of GTC or CPS), and in subjective memory function • Borderline significant improvement in attention/ concentration • Worsening in recall function Complications: Not provided
Hippocampal stimulation:[12] Cathodal transcranial direct current stimulation (3 and 5 days × 30 min, 2 mA) vs. placebo	• Drug-resistant MTLE with HS • 28 patients total • Mean age 37.8 (10.9)	Multicenter	2 months	• Significant reduction in number of seizures at 2 months (−48% in tx vs. −36% in placebo) Complications: Not provided

Continued

Table 3. Continued.

Intervention	Population	Study setting	Follow-up	Outcomes
Cerebellar stimulation:[35] Implanted 4-contact electrode on the cerebellar superomedial surface	• 5 patients with drug-resistant motor seizures: • 3 with stimulator ON and 2 with OFF in blinded phase	Single-center	Blinded randomized phase for 3 months followed by all ON	• Reduction in GTCs to 33% in ON vs. no change in OFF at 3 months Open label: • Mean seizure rate of 41% compared to baseline Complications: • Infection requiring removal of device in 1/5

AED, antiepileptic drug; AEP, adverse event profile; BDI, Beck Depression Inventory; BMP, Best Medical Practice; CES-D, Center for Epidemiologic Studies Depression Scale; CPS, complex partial seizure; eTNS, trigeminal nerve stimulation; GTC, generalized tonic-clonic seizure; HRQoL, health-related quality of life; HS, hippocampal sclerosis; LSSS, Liverpool Seizure Severity Scale; MCD, malformations of cortical development; MTLE, mesial temporal lobe epilepsy; NDDI-e, Neurological Disorders Depression Inventory—Epilepsy Scale; QOLIE-31, Quality of Life in Epilepsy Inventory; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SF, seizure frequency; SPS, simple partial seizure; tx, treatment; VNS, vagus nerve stimulation.

[a]Children allowed in protocol; yet, only adults enrolled.

Statistically significant improvements in QOL scores were also seen with RNS.[10,16] Treatment with the RNS system was not associated with cognitive decline when tested through 2 years. Small but significant beneficial treatment effects on naming were seen in patients with neocortical onset and in verbal learning for patients with mesial temporal lobe seizure onsets.[38]

Limitations of current neuromodulation RCTs

Different neuromodulation RCTs used different endpoints with each study, often evaluating multiple measures of seizure frequency and finding significant differences in one of these measures, but not the others. For example, whereas the positive results in the VNS pivotal studies in adults[14,31] centered on improvements in responder rates noted during the blinded study phase (24–27% in high-output stimulation arms vs. 6–15% in the low-output stimulation arms), there was no difference in responder rates with RNS at the end of the 3-month blinded phase (29% in treatment group vs. 27% in sham). Instead, the beneficial effects of RNS were supported by a better reduction in the mean percent change in seizure frequency during the blinded period (−37% in treatment vs. −17% in sham).[18] This variability in the choice of primary study endpoints makes it difficult to compare results historically among studies.

An additional confounding observation is the fact that most of reported benefits are observed in the open-label rather than blinded study phases, with similar results hovering at 50% reduction in seizure frequency regardless of whether thalamus, vagus nerve, cerebellum, hippocampus, or cortex is stimulated. Ongoing improvements in seizure frequency beyond the blinded study periods may suggest a cumulative benefit with further adjustments in the stimulation parameters, but the lack of a control limits the ability to ascertain the extent and mechanism of benefit truly attributed to each neuromodulation modality.

Finally, no RCTs compare different neuromodulation techniques among each other, despite significant variability in their risks and complications. The lack of comparative effectiveness data, particularly among studies that used heterogeneous populations (including some generalized epilepsy[6,17] or no description of epilepsy phenotype[9]), limits the ability to define the ideal device for a given patient.

The Evidence for Palliative and Ablative Procedures

Summary of available trials

Only one RCT was identified in this category, namely, the study by Barbaro et al.,[20,39,40] a prospective multicenter pilot study of gamma knife radiosurgery (RS) in adults with mesial TLE with hippocampal sclerosis, comparing low- (20 Gy, n = 17) versus high- (24 Gy, n = 13) dose radiation targeting the amygdala, hippocampus, and parahippocampal gyrus over a 3-year period (Table 1). No RCTs examine the safety and efficacy of corpus callosotomy aside from the study by Liang et al.[26] discussed above in the resective surgery section. There were also no RCTs identified for MST, consistent with a Cochrane review that reported no evidence for or against the use of MST in those with drug-resistant epilepsy.[41] Finally, although several recent HTAs were conducted to examine the safety and efficacy of LITT, they did not identify any RCTs of LITT for epilepsy.[19,42]

Benefits and risks of palliative and ablative procedures

The RCT of RS[20] reported seizure freedom in 76.9% (high dose) and 58.5% (low dose) of patients at 3 years. Neuropsychological outcomes were available on 26 patients at 2 years and were no different than at baseline. QOL improvements were reported in both groups. No differences

were reported in adverse events, including headaches, use of steroid, or visual field defects by dose, but one patient in the high-dose group experienced serious edema requiring urgent temporal lobectomy.

Limitations of radiosurgery

Unfortunately, the biggest limitation of the RS RCT is that the sample size is small, with incomplete follow-up at 2 years. This is challenging because outcomes may take up to 1–2 years to be achieved with RS unlike in the case of resective surgery where the results are typically immediate. Thus, excellent retention is necessary. Another limitation of RS is that, although two doses of radiosurgery were compared, it is unclear whether RS is noninferior or superior to resective surgery. Other advantages and disadvantages of RS and the other various surgical approaches discussed in this article are listed in Table 4.

Surgical Outcomes

Are surgical outcomes sustained in the long term?

Resective epilepsy surgery is far from a cure: 30–40% of patients undergoing a resection for frontal lobe epilepsy (FLE) are seizure free a decade after surgery,[43,44] whereas only 50–60% remain seizure free 10 years after TLE surgery.[43,45,46] Seizure recurrence is a complex, multifactorial, and dynamic phenomenon. Half of post-TLE surgery failures first manifest within 6 months of surgery, and half of ETLE surgical failures first manifest within 2–4 months of surgery; the remaining half of all surgical failures represent "late seizure recurrences" first manifesting several months to years after surgery.[47] Obvious causes of surgical failure such as inaccurate localization of the epileptogenic zone or incomplete resection of the known epileptogenic cortex are intuitive explanations of ongoing postoperative seizures. This prevailing concept of *inadequate resection* is variably illustrated by works attributing seizure recurrence after TLE surgery to: (1) existing or developing sclerosis in the hippocampus contralateral to the current resection,[48] (2) a remnant ipsilateral hippocampus,[49] (3) temporal-plus epilepsy defined by stereo-EEG suggestion of epileptogenic zone extension to the insula, orbitofrontal region, operculum, or temporoparietal junctions,[50] or (4) extension of the temporal epilepsy pathology to extratemporal components of the limbic network and the thalamus as suggested by functional or structural connectivity data.[51,52] Albeit variable in their "focus," these hypotheses share one common concept: in addition to the hippocampus, the epilepsy in failed TLE surgery is also "somewhere in the brain" outside of the mesial temporal structures, and the implied path to improving outcomes is in refining localization tools, making the resections bigger, or withholding surgery if the epileptic network is too widespread. Seizures that recur late, however, clinically behave like new-onset epilepsy rather than an incompletely resected focus of DRE. Late seizures are milder in severity and lower in frequency,[53–55] easier to control with AEDs,[54] and more likely to "run down" than their earlier counterparts.[54] Also, late seizure recurrences usually arise from the edge of the original resection in patients with normal preoperative brain MRI,[55] nonspecific surgical

Table 4. Comparison of surgical treatments for temporal lobe epilepsy

Surgical intervention	Advantages	Disadvantages
Anterior temporal lobectomy (ATL)	Supported by class I evidence; best seizure outcomes	Large incision and craniotomy; questionable neuropsychological implications of lateral cortex resection
Selective amydgalohippocampectomy (SAH)	Preservation of lateral cortex; smaller incision and craniotomy	Slightly worse seizure outcomes than ATL; still requires open surgery
Transsylvian approach	Complete preservation of lateral cortex	Technically challenging; damage to temporal stem
Transcortical approach	Technically less challenging	Damage to lateral cortex
Subtemporal approach	Avoids both sylvian fissure and lateral cortex	Possible retraction damage to basal temporal lobe
Gamma knife radiosurgery (RS)	No invasive surgery	Antiseizure effects delayed by 12–24 months
Stereotactic laser thermoablation (STA)[a]	Only burr hole required; preliminary favorable neuropsychological outcomes	Higher risk of persistent seizures than resection; long-term outcomes require further study
Device implantation	No brain resection	Palliative; worse seizure outcomes than resection/ablation
Responsive neurostimulation	Direct closed-loop therapy to EZ	EZ localization required; seizure freedom is rare
Vagus nerve stimulation	EZ localization not required	Seizure freedom is rare
Deep brain stimulation	EZ localization not required	Seizure freedom is rare

EZ, epileptogenic zone.
[a]Also referred to as LITT (laser interstitial thermal therapy).Reproduced with permission from Chang et al., *Epileb Behav* 2015.

pathology,[53] or long epilepsy duration.[43] This is in contrast to early recurrences, which usually localize to brain regions distant to the site of resection or to residual incompletely resected epileptic lesions, implicating a localization or resection challenge. A hypothesis of secondary epileptogenesis as a trigger for late recurrent seizures may account for the development of new epileptic tissue or the maturation of epilepsy in residual pro-epileptic cortex[47,56] and may thus open the door for alternative ways of improving outcomes through antiepileptogenesis strategies when such effective tools become available.

Surgery converts people from drug resistant to drug responsive

Inherent in our discussion so far is the idea that, in some cases, epilepsy is a dynamic process both *before* and *after* surgery. Before surgery, focal epilepsy matures over years to decades up to the point of drug resistance.[57] This is best illustrated in mesial TLE due to hippocampal sclerosis, where a "honeymoon" period of seizure freedom is typically seen on or off AEDs before drug-resistant seizures develop,[57] or in malformations of cortical development where, although the lesion is present at birth, seizures begin in teenage years or young adulthood.[58] Drug resistance is therefore a *time-dependent* process rather than an automatic consequence of a cortical lesion. Similarly, drug resistance is a *space-dependent* process whereby the extent of the epileptic network as defined by quantitative measures of cortical atrophy spreads beyond the physical epileptic lesion and inversely correlates with seizure control in new-onset epilepsy.[59–61] In this context, the mechanical process of removing the focus of DRE with epilepsy surgery interrupts but doesn't necessarily reverse molecular or structural changes that extend beyond the resection bed.[62] Consequently, *after* surgery, there is still a need in some cases for ongoing AED use to maintain seizure control. No randomized clinical trials adequately evaluated AED management after surgery, so the true "risk" of a breakthrough seizure due to AED withdrawal is unknown. However, observational data suggest that, although 17–25% of postoperative seizure recurrences occur with AED withdrawal, seizure control is regained after reinitiation of AEDs in 60–70% of these cases.[63–65] In that group of "seizure free but only while on AEDs," surgery *converted* DRE to a pharmacoresponsive disease. The notion that recurrent seizures with AED withdrawal reflect the burden of residual epileptogenicity is further supported by the observation that 70% of patients with seizure recurrence after AED discontinuation reachieved remission in one study of TLE surgery[63] as opposed to 50% of those whose seizures recurred while AEDs were simply being reduced: a lower threshold required for triggering recurrence thus translated into more difficulty with reattaining drug responsiveness. No clinical predictors could a priori predict patients whose seizures will recur during AED reduction as opposed to those whose seizures will recur after complete AED discontinuation.[63] Similarly, although low seizure frequency, lack of secondary generalization, unilateral preoperative EEG and MRI findings, and lack of need for invasive EEG recordings correlate with early seizure freedom after surgery for TLE,[46,53] only the presence of a specific pathological diagnosis predicts long-term seizure freedom: 40% of patients with gliosis or nonspecific pathology were seizure free 10 years after TLE surgery in the one series that investigated early versus late outcomes independently, as opposed to 80% of those with a specific pathological abnormality.[46] Overall, a lot remains to be understood about the determinants of cure (defined by seizure freedom off AEDs) or long-term seizure remission after epilepsy surgery.

Gaps In Knowledge

Having summarized so far the current highlights of surgical epilepsy RCTs, several challenges remain:

1 *The ideal surgical approaches for specific patient populations and epilepsy localization need to be defined.* As stated earlier, RCT evidence exists for the unquestionable superiority of resective surgery to medical therapy only in the context of TLE.[3,4] Beyond adult patients with TLE, all data driving surgical decision making are strictly observational. No surgical RCTs specifically address children.[29] Other striking challenges in need of rigorous research include:

- a Extra-TLE: The surgical data here are strictly retrospective but obviously favor surgical treatment in patients with clear lesions that can be completely resected, such as type II dysplasia, cavernomas, or low-grade brain tumors.[43,44] The long-term seizure and functional outcomes of resection in patients with normal brain MRI and suspected ETLE are less clear, as are the indications and protocols for choosing an ideal invasive EEG approach often necessary in these cases. A recent survey of nine major epilepsy surgery centers[22] shows that this challenging population of DRE patients with normal MRI currently represents the main patient population presenting for consideration of surgery, and that the proportion of invasive EEG recordings not followed by resections has more than tripled between 1991 and 2011. In an era in which multiple types of invasive EEG are available, including stereo-EEG, subdural electrodes, and combinations of subdural electrodes and depths, we should rigorously define criteria for choosing which technology to use and when the risk/benefit ratio of such evaluations, especially when invasive, is justified.
- b Selective amygdalohippocampectomy versus traditional temporal lobe resections, particularly in patients with preserved memory function: Limiting the

resection of the temporal stem and mesial structures is speculated to optimize neuropsychological outcomes, whereas including these structures in a standard temporal lobe resection is hypothesized by some to be necessary for optimal seizure outcomes.[66,67]

c Ablative versus resective strategies for temporal and extratemporal epilepsy also need further investigation.

2 *The indications and comparative effectiveness of the different neuromodulatory approaches* should be defined. Given the significant variability in cost, surgical risks, and complexity of postimplantation adjustments of stimulation parameters between vagus nerve stimulation, responsive neurostimulation, and thalamic stimulation, a better understanding of these questions is necessary.

3 *Understanding the mechanisms driving seizure outcomes is critical* given the current suboptimal seizure-freedom rates after resective surgery.[68] Approaches at improving outcomes should expand beyond improving epilepsy localization to understanding the mechanisms of postoperative epileptogenesis.[47,62] Such a paradigm shift in our approach at studying and working to modify surgical outcomes is necessary to avoid the stagnation of seizure-freedom rates at the 50% range in most types of resective epilepsy surgery.

4 Last, because evidence continues to suggest significant underutilization of epilepsy surgery, physician- and patient-related barriers to this effective treatment need to be better understood.[69,70]

Conclusions And Future Direction

Great advances exist in the field of epilepsy surgery, with a number of RCTs demonstrating the effectiveness of surgical therapy in those with drug-resistant epilepsy. Unfortunately, the generalizability of high-quality RCTs is limited because these are mostly applicable to persons with TLE. In other cases, populations are more heterogeneous, including RCT participants of various epilepsy etiologies and duration. Studies examining the effectiveness of limited versus more extensive resections often lack high-quality volumetric imaging studies pre- and postsurgery. Finally, reported outcomes are often limited, cannot be stratified by population owing to small sample sizes, are of short-term duration or vary considerably between studies.

Serious gaps exist regarding the effectiveness of epilepsy surgical therapies in those with ETLE, normal cognitive function, or nonlesional epilepsy. Our knowledge about the comparative effectiveness of various surgical therapies (resective vs. neuromodulating vs. ablative) and mechanisms of surgical outcomes is also limited. Finally, knowledge translation interventions among patients, caregivers, and health professionals are required to address the barriers to epilepsy surgery. To better understand barriers to epilepsy surgery recruitment and to facilitate participation and retention, future epilepsy surgery RCTs should consider a participatory action research approach so patients and their caregivers are involved in the study design and planning.

Future epilepsy surgery RCTs should have well-defined eligibility criteria, collection of standard outcomes and predictors, and long-term follow-up.[71] Because it can be impossible in some cases to entirely remove bias from certain epilepsy surgical RCTs (medical vs. surgical therapy), and because RCTs can be costly and difficult to perform, systematic and rigorous exploration of carefully collected and analyzed observational data (propensity modeling) may be required to answer at least some of the questions that remain unaddressed. Indeed, well-designed multicenter prospective observational studies may be the only feasible approach to determine the long-term outcomes of epilepsy surgery, an important gap in knowledge for the many young patients who undergo these procedures. This particularly concerns surgical procedures that are less commonly performed and populations in which epilepsy surgery is less often performed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Epilepsy surgery RCT.