TITLE

Surgical treatment for epilepsy: the potential gap between evidence and practice

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SUMMARY

Randomised controlled trials, along with more than one hundred case series and observational studies, support the efficacy and safety of resective surgery, and more recently non-resective interventions, for the treatment of drug resistant epilepsy in appropriately selected individuals. There is an argument that epilepsy surgery remains underused. The evidence to support this assertion is at times opaque. Recent longitudinal studies show a stagnant or decreasing rate of epilepsy surgery over time, despite the evidence and guidelines supporting its use. Some suggest that this stagnation is due to a decreasing pool of eligible surgical candidates. Others emphasise the numerous barriers to epilepsy surgery. Strategies exist to increase access and better communicate the efficacy of this potentially life-changing procedure. The further investigation of the nature and causes of the presumed underuse of epilepsy and the elaboration of strategies to address this treatment gap, are necessary and pressing.

Epilepsy affects at least 70 million people worldwide.[1] The prognosis for seizure remission for many individuals with epilepsy is favourable. In community-based cohorts, 60% of people will experience at least 5-years of remission during the first 9 years of their disease[2] although data suggests that this proportion may be much lower in people with focal, rather than generalised, epilepsy. [3]

Epilepsy is pragmatically defined as "drug resistant" when it remains uncontrolled despite two adequate trials of antiepileptic drugs (AEDs) that were appropriate for that person's epilepsy.[4] It is estimated that approximately 30% of individuals with epilepsy are drug resistant.[5] Such individuals are a great challenge for attending physicians. Not surprisingly, increased seizure frequency and severity, as well as AED polypharmacy are important drivers of health-related quality of life, resource use, and costs.[6] Eighty percent of direct and indirect costs of illness in epilepsy are accounted for by people with drug resistant epilepsy.[7] Premature mortality is more common in people with epilepsy as compared to the general population,[8] and individuals with more severe epilepsy are at greater risk of seizure-related injuries. Sudden unexpected death in people with epilepsy (SUDEP) is described as an important cause of epilepsy-related mortality.[9] The risk can be 0.9 per 1,000 person-years in low-risk populations,[10] but the odds of SUDEP increase by over 20-fold in those with uncontrolled convulsive seizures and AED polypharmacy.[11]

Since the initial work performed in the late 19th century, resective surgical procedures, excising putative epileptogenic foci, is an important intervention in the management of people with epilepsy.[12,13] Recent work emphasizes that epilepsy surgery can be a powerful means of treating people with drug resistant epilepsy, that it should not be viewed as a "last resort".[14] Despite our long familiarity with epilepsy surgery, a number of experts argue that epilepsy surgery remains underused.[15,16] Epilepsy surgery has been described as "arguably the most underutilized of all accepted therapeutic interventions in the entire field of medicine."[17]

In this Personal View, we discuss data addressing the efficacy, risks, and alternatives to resective epilepsy surgery. We then synthesize the evidence regarding patterns of use of epilepsy surgery, explore potential barriers, examine strategies to increase access to epilepsy surgery, and propose future directions for the study of this potentially life-saving, and life-changing, procedure.

The scope

We are acutely aware of the enormous epilepsy treatment gap, defined as the proportion of individuals who require but do not receive medical or surgical treatment, in low and middle-income countries (LMIC).[18] In many such countries, the epilepsy treatment gap is above 75%.[18] A World Health Organisation survey of health care providers carried out in 2005 reported that while there is an average of one neurologist per 100,000 persons in Europe and North America, this number plummets to less than one per million in sub-Saharan Africa and Southeast Asia.[19] Computerised tomography scans and electroencephalography are available in 96% and 92% of countries in the Americas, respectively, but only 67% and 78% of countries in Southeast Asia. The situation with respect to magnetic resonance imaging is particularly dire.[19] It is not surprising; therefore, that epilepsy surgery is performed in less than 20% of low-income countries.[19,20] Adherence to prescribed therapy is also particularly low in LMIC countries, related to availability, accessibility, and affordability of epilepsy-related healthcare resources, but also the lingering effects of the stigma of epilepsy, lack of awareness, and associated negative attitudes towards epilepsy and Western medicine. These issues make an examination of the use of epilepsy surgery in LMIC countries quite distinct. For this reason, as well as the dearth of data with reference to epilepsy surgery in such settings, we chose to focus this review primarily on high-income countries.

The benefits of epilepsy surgery

Seizure outcomes after resective surgery

Resective epilepsy surgery was first introduced in the late 19th century, although our modern approach, including the important role of electroencephalography, was developed later in the 1940's.[12,13] Over the ensuing decades, the practice of epilepsy surgery developed and expanded, its efficacy described in an ever growing number of case series and observational studies, of which there are now over one hundred.[21] The most cited randomized controlled trial (RCT) of epilepsy surgery compared the efficacy of anterior temporal lobectomy (ATL) to medical management alone in people with drug resistant mesial temporal lobe epilepsy.[22] In this single-centre study of 80 individuals, 23 of 40 (58%) individuals were free of seizures impairing awareness one year after surgery compared to 3 of 40 (8%) individuals in the medical group (intention to treat analysis). A more recent multi-centre RCT limited to individuals with newly diagnosed drug resistant epilepsy, failed to meet its recruitment target (n = 38) and was terminated early, but nevertheless showed that 11 of 15 (73%) of those in the surgical group were free of disabling seizures at two years' follow-up, as compared to no one in the medical group.[23]

There are also five other RCTs of resective epilepsy surgery comparing the efficacy of different surgical approaches rather than comparing surgical to medical management. Four of these RCTs compared resections of different extent in people with temporal lobe epilepsy (ie temporal lobectomy with or without sparing of the superior temporal gyrus, 2·5 vs 3·5 cm anterior temporal resection, temporal lobectomy with partial vs complete hippocampectomy, and temporal lobectomy with or without anterior corpus callosotomy in people with developmental delay).[24-27] None of these RCTs reported statistically significant differences in seizure outcome except for the study comparing temporal lobectomy with partial vs complete hippocampectomy where the proportion of seizure free participants was greater in the complete resection group [25 of 36 (69%) vs. 13 of 34 (38%)] without differences in neuropsychological outcomes.[26] Finally, an RCT of transcortical vs transsylvian selective amygdalohippocampectomy (SAH) did not find any differences in seizure freedom between both approaches but cognitive outcomes (improvement in fluency) were better in the transcortical group.[28] There remains controversy whether *en bloc* ATL and SAH are equally effective, with some meta-analyses showing SAH as more effective,[29] others that ATL is more effective,[30] and others with no evident difference.[31]

A recent Cochrane systematic review and meta-analysis of RCTs and observational studies showed that, after analysing 177 studies including 16,253 people, resective epilepsy surgery overall increased the probability of a person being free from seizures impairing awareness at one year by almost eight-fold and of being free from all seizures by 15-fold.[21] Overall, the quality of the included observational studies was judged to be very low while the first RCT to compare surgical to medical treatment[22] was judged to be of moderate quality.

The benefits of epilepsy surgery are not universal, varying to an important degree between different epilepsy populations. The existing RCTs comparing surgical to medical treatment were carried out in selected people with mesial temporal lobe epilepsy.[22,23] Subgroup analyses in the Cochrane review showed that the presence of mesial temporal sclerosis is associated with a 17% relative increase in the chance of good post-surgical outcome, while the absence of MRI evidence of a focal abnormality decreases the relative probability of good outcome by over

20%.[21] A separate meta-analysis drew a similar conclusion about the superior outcome among those with so-called “lesional” versus “non-lesional” epilepsy.[32] Lesser, but arguably still favourable, outcomes among those with non-lesional extratemporal lobe (ie, frontal, occipital, and parietal) epilepsy are reported, with an overall probability of seizure freedom one year or more post-surgery of 45% in adults[33] and 34% in children.[34]

Long-term post-surgical outcomes

There is less evidence about the long-term outcomes of epilepsy surgery. One prospective cohort study of 615 adults (the majority of whom underwent temporal lobe resections) showed that 52% of individuals remained free of disabling seizures five years after surgery and 47% at 10 years.[35] Seizure recurrence was two-fold higher among those with extratemporal resections as compared to those with ATLs. A meta-analysis of observational studies and case series (n = 71 studies, only six with a control group) showed that the overall long-term (ie, mean/median 5 years after surgery) probability of becoming seizure-free was 66% following temporal lobe resections (similar to the short-term outcome per-protocol analysis results of the seminal RCT[22]), 46% for occipital and parietal lobe resections, and 27% with frontal lobe resections.[36]

The accepted indications for an epilepsy surgery evaluation are given in Table 1.

Benefits beyond seizure frequency

The benefits of epilepsy surgery are not limited to seizure frequency. Epilepsy surgery was recently reported in the largest clinical cohort to result in a significant decrease in the mortality rate, as compared to people who did not undergo surgery.[37] This effect was most pronounced when examining those who were post-surgically free of generalised tonic-clonic seizures.[37] Simulation models suggest that epilepsy surgery increases life expectancy by an average of five years.[38,39] Other investigators demonstrate additional benefits to cognition,[40] social outcomes (eg, self-reported improvements in relationships, independence and overall lifestyle),[41] as well as psychiatric comorbidities.[42] Epilepsy surgery is also cost effective, associated with savings in direct medical costs of almost U$ 1,500 **per patient** over 18 to 24 months in one study [43] and as high as almost U$ 7,000 **per patient**-annum over an average of five years in another.[44]

The risks of epilepsy surgery

Medical and neurological complications

Most post-surgical complications in those who have epilepsy surgery are minor and tend to be associated with complete resolution.[45] According to one meta-analysis, major and minor medical complications occur in 2% and 5% of individuals.[45] Major medical complications include hydrocephalus and intracranial abscesses requiring surgical intervention. Minor medical complications are cerebrospinal fluid leaks, infection, aseptic meningitis, deep vein thrombosis/pulmonary embolism, pneumonia, intracranial haematomas, and metabolic disturbances. Major and minor neurological complications, on the other hand, occur in 5% and 11% of individuals. Minor neurological complications are those that resolve within three months of their onset while those that persist are considered major complications. The most common neurological complications are visual field defects involving one quadrant or less (occurring in 13% of persons) whilst 2% experienced hemianopia. Mild or temporary aphasia occur in 4% of individuals and more severe aphasia occur in less than 1%.[45] Complications tend to be more common in children and in those who undergo extratemporal resection.[45] Mortality is extremely rare.[45]

Neuropsychological and psychiatric complications

Apart from potential medical and neurological complications, there are possible neuropsychological sequelae to epilepsy surgery. One meta-analysis reported that among those undergoing ATL, verbal memory deficits occur in 44% of individuals post left-sided surgery and 20% post right-sided surgery.[40] Declines in visuospatial memory are reported in approximately 20% of individuals overall, irrespective of the side of surgery.[40] It is important to note that paradoxical gains in neuropsychiatric function are also reported: 7-14% for verbal memory and 10-15% for visuospatial memory.[40] Naming is decreased in 34% of left-sided surgeries but fluency is increased in 27%.[40] There have been reports of *de novo* mental health disease, especially among those with persistent post-operative seizures. These ranged from relatively mild conditions such as interictal dysthymic disorder among 18% of persons, to more severe psychosis but in only 1% of persons.[42] In general, however, studies report no changes or improvement in psychiatric outcomes after epilepsy surgery.[42]

Effects of medical centre experience

Most data on epilepsy post-surgical outcomes come from experienced, high-volume centres. Positive correlations between medical centre case volume and clinical outcome and mortality have been reported in oncological and cardiac surgery.[46,47] It is reasonable to question whether outcomes following epilepsy surgery in low-volume centres are as favourable as those in high-volume centres. Little data on this exist, with the exception of one USA study examining 6652 complete or partial lobectomies to treat epilepsy at 650 hospitals between 1990 and 2008. This study showed a statistically significant increase in the risk of post-operative adverse events when comparing high-volume centres (> 15 surgeries per annum) and low-volume centres (< 5 surgeries per annum), from 6·1% to 12·9%.[48]

Seizure reduction versus elimination after epilepsy surgery

More and more epilepsy surgery experts support the concept that epilepsy surgery seems to convert drug resistant epilepsy to drug responsive epilepsy. The proportion of people who are able to come off AEDs after surgery has not been studied prospectively or in an RCT. It is estimated, however, that up to 25% of people are seizure free and off AEDs after resective surgery,[49] which still leaves many who require ongoing management with AEDs to control their seizures or who prefer not to discontinue medical treatment. Seizure outcome after surgery is typically linked to the complexity of the epilepsy syndrome.[49] Similarly, the extent of the epileptogenic network on imaging is inversely related to seizure outcome in those with newly diagnosed epilepsy.[50] In cases of complex epilepsies, resective surgery likely interrupts the epileptogenic network but does not address molecular or structural changes beyond the resected site.[51] In such cases, seizures may recur after AED withdrawal or reduction, but in one study 75 of 112 (67%) became seizure free again after restarting AEDs, supporting the concept that surgery converted them from being drug resistant to drug responsive to AEDs.[52]

Alternatives to resective surgery

It is important to note the growing number of non-resective surgical approaches to treat drug resistant epilepsy introduced in recent years. These procedures include ablative interventions [gamma knife radiosurgery (one RCT),[53] laser interstitial thermal therapy (no RCT)][54] as well as neuromodulation interventions such as cerebellar stimulation (one RCT),[55] hippocampal stimulation (two RCTs),[56,57] repetitive transcranial magnetic stimulation (one RCT),[58] responsive neurostimulation (one RCT),[59-61] thalamic stimulation (one RCT),[62] trigeminal nerve stimulation (one RCT),[63] and vagal nerve stimulation (six RCTs).[64-69] These interventions are evolving rapidly and for some individuals represent a less invasive and a more acceptable approach as compared to resective surgery. Table 2 demonstrates the advantages and disadvantages of various resective, ablative and neuromodulatory approaches used in the treatment of temporal lobe epilepsy.[70] Unfortunately, despite the effectiveness of some non-resective interventions, the heterogeneous reporting of seizure outcome (different endpoints) between ablative and neuromodulation studies makes it impossible to determine the comparative effectiveness of these devices and an RCT comparing their effectiveness to resective surgery is lacking. It is likely as a result of this lack of evidence that resective surgery represents the great majority of surgical interventions in epilepsy.[71] For this reason, we focus on resective approaches in our evaluation of the use of epilepsy surgery.

The use and underuse of epilepsy surgery

The epilepsy surgery treatment gap

Evaluating how the provision of resective epilepsy surgery compares to the requirements of those with drug resistant focal epilepsies has proven to be a great challenge, with discordant results. An often cited report on the epilepsy surgery treatment gap concluded that "surgical activity" must more than triple again just to accommodate the annual increment, let alone to address the backlog."[72] This conclusion was based on the comparison of the number of epilepsy surgeries reported in a 1992 voluntary survey of large number of USA epilepsy centres, to a 1990 National Institutes of Health estimate of the nationwide number of surgical candidates.[73] One prospective survey of all adult and paediatric epilepsy surgeons in the UK, on the other hand, found that the 422 surgeries performed in 2000 were, when compared to estimates derived from the UK National General Practice of Epilepsy, almost sufficient to at least accommodate the estimated 450 new surgical candidates who accrued over this same period.[74] A recent retrospective population-based cohort study using administrative data showed that only 1·2% of individuals with drug resistant epilepsy underwent epilepsy surgery during a two-year observational period.[75] This study had limitations, however, as have been outlined by others[76] and was unable to provide a sense of how this surgery rate corresponded to population requirements. Other research groups report that approximately 1·5 to 3% of individuals in the general population with incident epilepsy require epilepsy surgery[74,77] although much work to further examine the number of potential surgical candidates in the general population is still required.

Referral patterns for epilepsy surgery

Direct evidence of the underuse of epilepsy surgery is sparse. There is, however, definite evidence of under-referral and significant delays in the referral of suitable candidates for epilepsy surgery evaluation. A 2001-2002 population-based Swedish study demonstrated that of 88 individuals with severe focal epilepsy in a relatively closed population, up to 40% were not appropriately referred to an epilepsy centre.[78] A Dutch cross-sectional study in 10 hospitals showed that 63% (116 of 185) of prevalent “candidates for screening” were similarly not referred.[79] Intractable epilepsy becomes evident within an average of nine years after disease onset[80] but the referral delay for a surgical evaluation is approximately 20 years in adults.[80-82] This referral delay has remained largely stable over the last several decades,[81] or even slightly increased.[83,84]

Some of the apparent underuse of epilepsy surgery may reflect that epilepsy is a dynamic condition in some, alternating between drug responsive and drug resistant states. Temporary remission may reduce enthusiasm for epilepsy surgeryfor many individuals and health professionals. An often cited report describes that among those with previously untreated epilepsy, 60% will become seizure-free for at least one year, during a median period of five years, while treated with either their first or second AED.[5] Twenty percent of such individuals, however, who do not respond to either their first or second AED will go on during a seven-year period to enjoy at least one-year terminal remission of their epilepsy; a further 30% will experience a 50% reduction in their seizure frequency.[85] According to one study, approximately 5% of people who fail to respond or tolerate at least two AEDs go on to achieve a 6-month terminal seizure remission annually, with further medication adjustments.[86] On the other hand, epilepsy remains unpredictable and seizure-remission may be short-lasting. Among people with epilepsy and five years of seizure freedom in one clinic-based series, 40% went on to have at least one recurrent seizure.[87] A community-based and prospective cohort study examining cases of incident epilepsy reported that almost 60% of children entered into a one-year remission but that 70% of them later relapsed during a median follow-up period of 10 years.[88]

Temporal trends in epilepsy surgery

Not necessarily evidence of underuse but important insights are nevertheless gained from an examination of temporal trends in the practice of epilepsy surgery. Administrative data from the Nationwide Inpatient Sample (NIS), which includes databases from a 20% random-sample of all non-federal USA hospitals, collected between 1998 and 2008[89] and 2009,[90] reported that the use of epilepsy surgery has failed to increase over time. This was found despite a paradoxical increase in the number of hospitalizations for focal epilepsy, which doubled over this same time period, to approximately 8000 per year (Fig. 1a).[89,90] A UK survey of adult and paediatric epilepsy surgeons (a follow-up study to the 2000 survey described above)[74] not only failed to show an increase in the number of surgeries, but instead reported a meagre 246 surgeries (excluding vagal nerve stimulators) nationwide over a 12-month period in 2010-2011, a dramatic 40% decrease from 10 years prior.[71] Data from the Swedish National Epilepsy Surgery Register demonstrated a similar decrease in the number of surgeries per annum over time, from 78 in 1991 to 50 in 2007.[91]

It is important to note that much of the data available on current utilisation patterns for epilepsy surgery are drawn from retrospective administrative databases which are prone to misclassification errors due to difficulties in identifying individuals with incident epilepsy (versus prevalent cases), those with drug resistant epilepsy, and those who have previously undergone epilepsy surgery; higher quality data are therefore urgently required. Any changes or lack thereof, in the rate of epilepsy surgery may be due to fluctuations in spurious observations rather than actual outcomes. Other potential explanations for the observed temporal trends in epilepsy surgery exist (Table 3). One possibility is that the observed trends result from a shift in where epilepsy surgery is performed, from a small number of high-volume centres to a larger number of low- and middle-volume centres. For example, data from US hospitals showed that between 1990 and 2008 the number of hospitalisations increased more than two-fold more at low- and middle-volume centres (performing less than five or 15, respectively, procedures per year), as compared to high-volume centres, with a corresponding shift in the number of lobectomies (Fig. 1b).[48] Such lower-volume centres appear to operate on a smaller proportion of hospitalisations,[48] which may be as a result of insufficient resources and expertise.[92]

Some investigators suggest that the apparent reduction in the use of epilepsy surgery over time is also potentially due to a depletion of eligible candidates for epilepsy surgery from the general population.[71] Indirect evidence of this may be the decreasing number of standard temporal lobe surgeries performed[84,93,94] despite the greater use and availability of video-EEG monitoring.[90]

The increasing delay between epilepsy onset and surgery reported by some[83,84] may also indicate a depletion of optimal candidates and an increasing focus on more challenging cases, an opinion held by many experts.[95] The pool of surgical candidates may be depleting as a direct result of the increasing success of medical treatment. Some evidence exists to support a modest improvement in efficacy when comparing newer to older generation AEDs.[96-98] It could also be argued that with a greater number of AEDs currently available in the armamentarium the total number of people who benefit from drug treatment has increased even if the results from each individual drug are modest. The pool of adult surgical candidates may also be decreased due to successes in paediatric populations. In the face of stagnant or decreasing rates among adults, the rate of epilepsy surgery among children has increased over the last few decades.[90,93,99] Of 3,621 procedures reported in 2012 by one USA study, 1,110 were among children.[93] Over 12 months (2010-2011) in the UK, 238 procedures were performed in children and 472 were performed in adults.[71] It has been suggested that improved management of febrile seizures and febrile status epilepticus in children has also helped decrease the number of adults with drug resistant epilepsy,[93] which may explain the particular decrease in surgery for mesial temporal sclerosis (MTS) over time which has been observed by a number of investigators.[84,93,94]

Any proposed decrease in the pool of eligible, and identified, candidates for epilepsy surgery is not discordant with its persistent underuse. Such an observation may reflect that the identified and generally considered pool of eligible individuals is decreasing all the while an even larger pool of individuals, who would be potential candidates, never receive the consideration they are due.

Factors that influence use of epilepsy surgery

Facilitators to surgery

Definite estimates on the use and probable underuse of surgery are sparse but evidence exists reporting many barriers and, less so, facilitators to epilepsy surgery. Patient facilitators to surgery include that they are more disabled by their epilepsy (more frequent and severe seizures, frustration with epilepsy, stigma, embarrassed to have seizure in public, etc.)[100] and have a strong desire to be seizure-free to improve their psychosocial outcomes (eg, work and driving opportunities).[101-104] The availability of less invasive surgical approaches as discussed earlier (ablative, neuromodulation) with potentially similar effectiveness (better or same seizure outcomes and less adverse events) is a promising facilitator to epilepsy surgery that requires further investigation.

Barriers to surgery

There are strikingly more barriers than facilitators to epilepsy surgery. The main barriers to epilepsy surgery usually originate from the patient/family or from the physician/health system, though societal barriers also exist (Table 4). Barriers to epilepsy surgery include lack of knowledge and misconceptions about epilepsy surgery, behavioural and cultural issues, access issues, and research gaps. There are also significant disparities in care related to epilepsy surgery. Fear and anxiety are major factors influencing individuals' decision to proceed with surgery.[100,104,105] This is presumably in large part driven by a lack of knowledge and by the observation that many overestimate the risk of surgery.[14,106] People with epilepsy describe it often as a very dangerous intervention that should only be considered as a last resort measure, including 73% of those in one Italian study.[100,104,105,107-110] Mistrust of physicians likely plays a major influence as well.[105] In one Canadian study, however, more than 90% of participants reported that they generally trust their physician.[108] In a smaller USA study, people listed their epilepsy physician (52·2%) followed by their neurosurgeon (34·8%) as the main source of information about epilepsy surgery and indicated that their epilepsy physician was the most influential in their decision to pursue surgery.[100] It is thus imperative for physicians to be well informed about the risks and benefits of epilepsy surgery as they can play a major role in helping individuals reach an informed decision with regards to epilepsy surgery that is devoid of misconceptions.[108] There is, however, a serious knowledge to action gap about the benefits of epilepsy surgery among physicians who are not epilepsy specialists, including some neurologists, and many still do not refer people with epilepsy for surgical consideration or have negative attitudes towards or misconceptions about the risks of epilepsy surgery.[14,106] For example, 30% of children in one USA study were referred by a non-neurologist directly to a neurosurgeon for epilepsy surgery consideration rather than an epileptologist.[107] One study in Michigan found that 11% of neurologists who responded to the survey (response rate 20%) never discuss epilepsy surgery with their patients and almost 20% said that all AEDs had to fail before considering an individual to be drug resistant.[111] This is concordant with an Italian study that reported that 60% of child neurologists do not follow treatment guidelines for epilepsy.[110] Many child neurologists reported not recommending surgery even when MTS-like changes are present on MRI as well as suggesting that an individual should only be referred after failing at least five AEDs.[110] A recent Canadian study found that almost 22% of people with epilepsy had previously been discouraged from having epilepsy surgery, with neurologists as the main culprits 65% of the time.[108] In most cases, however, neurologists discouraged surgery because the patient was not a surgical candidate. Epilepsy was more often inappropriately discouraged by a family member (eg, “Father suggested I wait a few years since science always is learning new techniques…”;

"Family and friends were concerned of dangers") or the patient was "hoping for less invasive treatment".[108]

Other individual and societal factors that can be barriers to epilepsy surgery include stigma and negative attitudes towards epilepsy per se, poor access to care (ie, lack of transportation, inability to take time off of work or school, forgetting appointments due to cognitive deficits), depression/other comorbidities, and poor self-efficacy and self-management (Table 4).[106]

Health system factors also contribute to the delay and/or underuse of epilepsy surgery. These include a lack of access to comprehensive epilepsy surgery centres, a problem that is particularly evident in low- and middle-income countries, where up to 80% of countries are yet to have tertiary and quaternary epilepsy care programmes.[112] Issues with inadequate health resources, however, are prominent even in high-income countries, as shown in a Canadian national survey of neurologists where more than 75% of respondents identified this as the biggest barrier to epilepsy surgery.[113] Perceived lack of communication between tertiary care epilepsy centres and community-based practices is also a potential barrier to referral for epilepsy surgery.[14]

There are important disparities in epilepsy surgical care that require further exploration as well. In a number of USA studies, older people, those of African-American descent (also "non-whites"), those with limited English-language proficiency, and those without private insurance represent a disproportionately small proportion of those who undergo surgery.[89,100,114] A number of reasons for disparities by race include distrust of physicians, language barriers, and socioeconomic status (SES).[106] Disparities in access to epilepsy surgery by insurance status are particularly evident in the USA where uninsured individuals rely on government programmes such as Medicaid. The above vulnerable populations have lower odds of undergoing epilepsy surgery, even in well-designed studies where key confounders are adjusted for.[89,100,114] Even in

Canada where universal health care exists, increased delays in time to surgery were reported in children of lower SES.[115] The authors also found that children of lower SES had poorer seizure outcome.[115] Those with a lower IQ are generally less likely to have epilepsy surgery, though the proportion of those with an IQ < 70 who underwent epilepsy surgery in London, UK study increased from 3% to 10% pre and post 2000 (1988-2007).[116] These barriers and disparities provide a strong foundation to guide future implementation strategies to address the many misconceptions about epilepsy surgery and to close the knowledge to action gap for those with epilepsy who may benefit from this efficacious intervention.

Strategies to improve knowledge and referrals

Patient and caregiver approaches

Strategies to improve referrals for epilepsy surgery, using a multifaceted approach, are outlined in Fig. 2. Ultimately, the best way to develop a successful implementation strategy is to involve the target users early on. In people with epilepsy and their family/caregiver(s), knowledge can be increased using a variety of knowledge translation tools including online educational materials, written information in physician offices, webinars, podcasts, patient testimonials video, regional educational sessions, and social media. It is important to also educate the individual and their families about self-efficacy and self-management as having such skills will not only break down barriers to epilepsy surgery, but should also improve their overall health outcomes. Comorbidities should be managed in persons with epilepsy, especially depression, since it can otherwise be associated with poor adherence to treatment, increased seizure frequency, higher health resource utilization, and self-efficacy.[117] Stigma interventions are also needed at every level (patient, family, health professionals, and society) to remove barriers for people with epilepsy.

Clinician and health system approaches

For physicians, the implementation of best practices often occurs using clinical practice guidelines (CPGs). A number of CPGs for epilepsy exist, although relatively few with direct reference to epilepsy surgery.[118] One of the first major formal CPGs in epilepsy surgery was published in 2003, under the auspices of the American Academy of Neurology, American Epilepsy Society, and American Association of Neurological Surgeons. This CPG recommended that individuals with "disabling complex partial seizures" be referred to an epilepsy surgery centre after failing to respond to AED therapy.[119] Consensus statements and CPGs regarding epilepsy surgery have been published for paediatric populations[120] as well as local organisations in the UK,[121] France,[122] and India.[123]

Clinical practice guidelines improve processes of care and outcomes.[124] They are, however, often poorly implemented, including in epilepsy, and still represent an "elusive target."[82,125,126] One strategy to improve their implementation is to incorporate them into electronic medical records (EMRs) and/or at the point of care. A systematic review found that the implementation of electronic CPGs improved universally processes of care.[127] Ultimately, the only effective way to ensure guidelines are used in practice is to adapt them to the local context. A great framework that can be used to achieve this goal is the knowledge to action gap framework from the Canadian Institutes of Health Research in conjunction with the ADAPTE process, which involves decision-makers and end-users in the implementation process.[128,129] Other strategies to increase knowledge about epilepsy surgery for physicians include prompts embedded in EMRs, online tools, webinars, and podcasts. Pay per performance programmes can help "persuade" physicians about the importance of adhering to best practices. Participation of physicians in mobile clinics and telehealth can also increase access to care for persons with epilepsy, to facilitate the road to epilepsy surgery.

Another approach to improving access to epilepsy surgery by targeting physicians is to provide innovative, evidence-based means of predicting post-surgical outcome**.** Predictors of post-surgical freedom have been described.[130] Recently, investigators began to translate this knowledge into more clinically useful instruments, in the form of predictive scores[131,132] or graphical nomograms.[133] The goal is that such instruments will encourage and facilitate primary and secondary care providers to refer potential candidates for an evaluation at a tertiary or quaternary epilepsy centre. Similarly, clinical decision making tools can also facilitate clinical care. An online clinical decision tool was developed (www.toolsforepilepsy.com) to assist physicians who are not epilepsy experts in determining who should be referred for an epilepsy surgery evaluation.[134] The tool is publically available, easy to use, and its feasibility (Canada and Germany) was determined to be very good.[135,136] The tool is now being translated into 15 languages, with its broad implementation across Canada and Europe in planning, although its final impact on clinical practice remains to be studied. Nevertheless, many examples of the successful implementation of clinical decision rules in neurology, especially in the stroke field, exist and suggest that such tools can improve outcomes with the right implementation science strategy.[137,138]

Society and community-level approaches

Strategies at the community/societal level must also be considered to increase access to epilepsy surgery (Fig. 2). Engaging lay organizations to help promote health policy in collaboration with medical professional organization can be beneficial. A number of key policies such as antidiscrimination policies at work, in schools, and sick leave policies should be considered.[106] Improved public transportation with discounted fares would help reduce transportation barriers so those with epilepsy who cannot drive can still attend medical appointments.[106] Increased funding for research to develop better diagnostic tools to clearly delineate the epileptogenic zone and to determine the comparative effectiveness of less invasive surgical approaches relative to resective surgery would be beneficial. Improved seizure outcomes using less invasive interventions with minimal adverse events (e.g. better cognitive outcomes) would promote utilization of epilepsy surgery.

Future directions

Among carefully selected candidates, epilepsy surgery is efficacious and safe. There is a persistent and likely underuse of epilepsy surgery. There is evidence of under- and delayed-referral of potentially appropriate individuals with drug-resistant epilepsy. High quality population-based data remain sorely needed to determine the true proportion of those with epilepsy who are possible surgical candidates and who do or do not undergo successful epilepsy surgery. Without a carefully designed prospective study where multiple sources of ascertainment are used along with collaboration from an interdisciplinary team (from primary care to neurosurgeons), we may never know the answer to the questions: Is the rate of epilepsy surgery really decreasing and, if so, why? How many people with epilepsy are never referred to a neurologist for epilepsy care? How many are followed by neurologists, are appropriate surgical candidates, but are never referred to an epilepsy centre? When individuals are referred and deemed appropriate candidates for surgery, why do they sometimes decline to have surgery? This needs to be carefully documented at the point of care.

There is also an urgent need to close the knowledge to action gap and break down the barriers to epilepsy surgery by following an integrated knowledge translation multipronged intervention approach[107] (including decision aids for individuals and physicians)[104] where people with epilepsy, support groups, physicians, policy makers, and researchers work together to ensure that those who are appropriate for epilepsy surgery are referred in a timely manner, using a shared decision-making process. This will also require improving education to reduce physician misconceptions about surgery, and patient education to reduce the fears and anxiety they face surrounding epilepsy surgery.[103] We have at our disposal what is an efficacious treatment although our knowledge about the comparative effectiveness of various surgical therapies is limited. Nevertheless, in those in whom epilepsy surgery is appropriate, it is our obligation as a community to ensure that it is used to the fullest possible extent, to both change and save individuals' lives.

Search Strategy

We searched the electronic database PubMed (up to May 31, 2016) with the following keyword search strategy: (epilep* or convuls* or seizure*) AND surgery AND (underutilization OR underutilization OR utilization OR utilization OR underuse OR delay OR timely OR dispariti* OR treatment gap OR barrier* OR perception* OR attitude* OR decision-making OR prognostic tool OR decision analysis or comorbid*). The search was not limited by language of publication. Our search identified 1672 records. The title and abstract of each record were screened by one author (NJ). Additional articles were identified from the authors' own files and from chosen bibliographies. The articles in this Review were included at the authors' discretion on the basis of originality and relevance of the publication.

LEGENDS

Figure 1: Temporal trends in epilepsy surgery

A) Data from the Nationwide Inpatient Sample, which includes databases from a 20% random-sample of all non-federal USA hospitals, reported that the absolute number of lobectomies for epilepsy has not increased over time while the number of hospitalisations for focal epilepsy has paradoxically increased. The dashed line represents the year of publication of the first randomised controlled trial of epilepsy surgery.[22] Reproduced from Englot,[89] by permission of Wolters Kluwer.

B) The number of epilepsy surgeries performed at high-volume epilepsy centres has decreased over time, while the number of hospitalisations for focal epilepsy at low-and middle-volume centres has increased by 235-300%. These hospitalizations in low- and middle-volume centres, however, less often result in a lobectomy, relative to high-volume centres. Reproduced from Englot,[48] by permission of the American Association of Neurological Surgeons.

Figure 2: Strategies to increase referral for epilepsy surgery

Footnote: *including self-efficacy and self-management tools; **consider electronic clinical practice guidelines; EMR = electronic medical record; MD = medical doctor; mgt = management; PWE = person with epilepsy

Table 1: Indications for an epilepsy surgery evaluation[16]

- Any patient with drug resistant epilepsy
- Any patient with a complex epilepsy syndrome or requiring a complex surgical intervention for epilepsy
- Patients with stereotyped seizures who also have focal findings (on EEG, MRI brain, etc.)
- Any child with a surgically accessible MRI lesion with or without seizures

Table 2: Resective and non-resective interventions for temporal lobe epilepsy

	Advantages	**Disadvantages**
Anterior temporal lobectomy[22,23]	Supported by class I evidence; best seizure outcomes	Largest incision and craniotomy; questionable neuropsychological implications of lateral cortex resection
Selective amygdalohippocampectomy[28-31]	Preservation of lateral cortex; smaller incision and craniotomy	Possibly 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 surgery[53]	No invasive surgery	Antiseizure effects delayed by 12-24 months
Stereotactic laser thermo-ablation[54]	Only burr hole required; preliminarily favourable 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[59-61]	Direct closed-loop therapy to EZ	EZ localisation required; seizure freedom is rare
Vagus nerve stimulation[64-69]	EZ localisation not required	Seizure freedom is rare
Deep brain stimulation[62]	EZ localisation not required	Seizure freedom is rare

Reproduced from Chang,[70] by permission of Elsevier.

EZ: epileptogenic zone

Table 3: Possible explanations for the apparent decrease in epilepsy surgery

- Spurious observations due to incomplete or biased data
- Decreasing facilitators and/or worsening barriers
- Depletion of eligible candidates from the general population
    - Improved efficacy of newer generation antiepileptic drugs[96-98]
    - Increasing number of successful surgeries among children[90,93,99]
    - Improved management of febrile seizures and febrile status epilepticus[84,93,94]
- Redistribution of pre-surgical evaluations from high-volume centres to low- and middle-volume centres
    - As compared to high-volume centres, these are less likely to proceed to surgery due to more limited resources and expertise[48,92]

Table 4: Possible barriers associated with epilepsy surgery

	Barriers

Patient/family factors	• Lack of knowledge about and misconceptions about epilepsy surgery
	  ○ Lower educational attainment[105]
	  ○ Poor health literacy and language barrier[106]
	  ○ Self-perceived stigma[106]
	  ○ Misconceptions, fear and anxiety about risks of epilepsy surgery[14,100,104-109]
	• Poor behaviours/cultural issues
	  ○ Poor self-efficacy[106]
	  ○ Poor self-management[106]
	  ○ Parents wanting their children to be old enough to be involved in surgical decision making[110]
	  ○ Mistrust of physician[105,106]
	• Access issues
	  ○ Lack of transportation[106]
	  ○ Unable to miss work[106]
	  ○ Unable to miss school[106]
	  ○ Lack of child care to attend appointments/be admitted[106]
	  ○ Disparities
	    ▪ Age (less likely to be operated if older)[100,114]
	    ▪ Race (less likely to be operated if non-white)[89,100,114]
	    ▪ IQ (less likely to be operated if lower IQ)[116]

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Comorbidity (e.g. psychiatric comorbidity often higher in non-surgical group)[100,106]
Insurance status (e.g. shorter time to surgery and greater odds of receiving surgery if private insurance versus Medicaid)[89,100,114]

Research gaps

Insufficient knowledge and/or understanding about mechanisms responsible for refusal to have epilepsy surgery

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<td>Physician/health system factors</td>
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Lack of knowledge about and misconceptions about epilepsy surgery[14,106,110,111,113]

Definition of drug-resistance
Indications for epilepsy surgery
Misconceptions about surgical risks

Poor behaviours/cultural issues

Negative attitudes about epilepsy surgery[105]
Not referring due to:[108]

No benefits if refer
No means to increase capability or opportunity
Lack of environmental resources to facilitate referrals

Poor patient-physician relationship
Poor communication between epileptologists and community physicians (i.e. primary care and neurologists)[14]

Access issues

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	○ Lack of epilepsy surgery programme in their region ○ Inadequate health resources[112,113] ○ Complex health insurance programmes/policies • Research gaps ○ Need better diagnostic tools to more optimally delineate extent of epileptogenic zone ○ Lack of comparative effectiveness studies about surgical approaches (e.g. resective vs neuromodulation vs ablative) ○ Lack of evidence regarding optimal extent of resection to optimize seizure outcome but minimize adverse events (e.g. SAH vs temporal lobectomy?) ○ Need more non-invasive surgical approaches

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AUTHORS CONTRIBUTIONS

NJ: Original concept, drafting, and revision of manuscript.

JWS: Original concept and critical revision of manuscript.

MRK: Original concept, drafting, and revision of manuscript.

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