

Randomized Trials and Collaborative Research in Epilepsy Surgery: Future Directions

Samuel Wiebe, Nathalie Jette

ABSTRACT: Background: Although randomized controlled trials (RCTs) are the gold standard for evaluating therapeutic interventions, surgical RCTs are particularly challenging and few have been done in the field of epilepsy surgery. We assess the level of RCT activity in epilepsy surgery and propose feasible alternatives to develop sustainable research initiatives in this area. **Methods:** We undertook a systematic review of the world literature to assess the level of RCT activity in epilepsy surgery. Previous personal experience with RCTs in epilepsy surgery and examples of successful Canadian multicentre research networks were reviewed to propose initiatives for sustainable, valid research in epilepsy surgery. **Results:** We identified 12 RCTs in epilepsy surgery, including 692 patients, of whom 416 were involved in vagus nerve stimulation, 16 in various brain electrostimulation procedures, 180 in comparisons of different surgical techniques, and 80 in a comparison of medical versus surgical therapy. Most studies were of short duration (median = 3 months, range 3-12 months). In the area of resective surgery, only temporal lobe epilepsy has been subjected to any type of RCT comparison. All RCTs have been done within the last 13 years. There were no multicentre Canadian surgical studies. **Conclusions:** The adoption of RCTs in epilepsy surgery has been slow and difficult worldwide. Because of its universal health care system and its well established epilepsy surgery centres, Canada is in a strong position to create a national epilepsy surgery research initiative capable of undertaking high quality, sustainable research in epilepsy surgery.

RÉSUMÉ: Les essais randomisés et la recherche en collaboration en chirurgie de l'épilepsie : orientation. Contexte : Bien que les essais contrôlés randomisés (ECRs) soient l'étalon or pour évaluer l'intervention thérapeutique, les ECRs chirurgicaux posent un défi particulier et peu ont été faits dans le domaine de la chirurgie de l'épilepsie. Nous avons évalué le niveau d'activité ECR en chirurgie de l'épilepsie et nous proposons des alternatives réalisables pour développer des initiatives de recherche viables dans ce domaine. **Méthodes :** Nous avons effectué une revue systématique de la littérature mondiale afin d'évaluer le niveau d'activité ECR en chirurgie de l'épilepsie. Nous avons revu notre expérience personnelle antérieure dans ce domaine et des exemples de recherche multicentrique en réseau au Canada qui ont été couronnées de succès afin de proposer des initiatives viables et valides dans ce domaine. **Résultats :** Nous avons identifié 12 ECRs en chirurgie de l'épilepsie auxquelles 692 patients ont participé, soit 416 patients qui ont participé à des études sur la stimulation du nerf vague, 16 à des études sur l'électrostimulation cérébrale par différentes techniques, 180 à des études de comparaison de différentes techniques chirurgicales et 80 à des études comparant un traitement médical à un traitement chirurgical. La plupart des études étaient de courte durée (médiane de 3 mois, fourchette de 3 à 12 mois). En ce qui concerne la résection chirurgicale, seule la chirurgie pour épilepsie temporale a fait l'objet d'ECRs. Tous les ECRs ont été faits au cours des 13 dernières années. Il n'existe pas d'étude chirurgicale canadienne multicentrique. **Conclusions :** Le recours aux ECRs dans le domaine de la chirurgie de l'épilepsie à travers le monde est un processus lent et difficile. Le Canada est dans une position privilégiée pour créer une initiative de recherche nationale dans ce domaine. Il possède un système universel de soins de santé et des centres de chirurgie de l'épilepsie qui sont bien établis, ce qui permet d'entreprendre une recherche viable, de haute qualité.

Can. J. Neurol. Sci. 2006; 33: 365-371

Over the years, clinicians have wrestled with the optimum methods to deal with bias and confounders in clinical research. Among the many types of biases, two can dramatically influence the study results and are particularly important in assessing the effect of surgical interventions. Selection bias refers to the process by which participants are not selected equally for the treatment and the control groups, resulting in groups with different prognostic variables. The best way to avoid selection bias is through concealed randomization, a process by which each study participant has an equal chance of being allocated to the experimental or to the control group. The second type of bias

pertains to outcome assessment. This entails a risk of treating patients or assessing outcomes differently, based on expectation and preconceptions of the treating and the evaluating

From the Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada.

RECEIVED FEBRUARY 21, 2006. ACCEPTED IN FINAL FORM MAY 20, 2006.

Reprint requests to: Samuel Wiebe, Foothills Medical Centre, 1403-29th Street N.W., Calgary, Alberta, T2N 2T9, Canada.

individuals. The optimum way to deal with outcome assessment bias is through blinding or masking of study participants, treating clinicians, outcome assessors and data entry personnel. Some researchers estimate that inadequate concealment of randomization may result in an over estimation of benefit of up to 40%, and that lack of adequate blinding may over estimate results by 17%.¹ Recently, minimization has been used as a statistical method to ensure similarity of groups based on predefined prognostic criteria.²

The methodology of clinical research in epilepsy surgery has evolved substantially in the last 15 years. Observational surgical studies have adopted increasingly rigorous methods of data gathering and reporting. Although few surgical studies have controls, modern reports have strengthened their validity, and centres around the world document very similar surgical results.³ Randomized controlled trials (RCT), however, remain sparse despite the large number of surgical interventions and devices used in the treatment of epilepsy. The challenges imposed by RCTs of surgical interventions, particularly in epilepsy, have been reviewed.⁴ Most notably these include willingness of patients and clinicians to allocate patients to surgery at random, issues with equipoise (insufficient uncertainty about the risk and benefit of alternate treatments), and difficulties with blinding or masking study participants. Although some neurosurgical studies have used sham brain operations, especially in the treatment of movement disorders,⁵ heated ethical debate precludes its widespread adoption.⁶

In this review, we systematically appraise the RCT addressing aspects of surgical procedures or devices in the treatment of epilepsy, or aspects of management of medical issues in relation to surgical interventions in epilepsy. Lastly we propose feasible initiatives to develop and sustain high quality surgical research in epilepsy in Canada.

METHODS

We performed an extensive literature search using Medline and the Cochrane Database, spanning the years 1966 to 2005, using MeSH terms and text words involving epilepsy, surgery, surgical treatment, vagus nerve stimulation, deep brain stimulation, hippocampal stimulation, responsive neuro-stimulation, cerebellar stimulation, neurosurgery, and limiting it to humans and "RCTs". We also searched references of relevant papers. Studies were included if they were RCTs describing the efficacy of therapeutic surgical procedures, surgical devices, or medical management around surgical interventions in epilepsy. Results were tabulated and summary statistics were derived from each study. When possible, we calculated the number needed to treat (NNT), which refers to the number of patients that need to undergo the procedure for one additional patient to benefit. In addition, we provide a brief description of the trials' methodology, duration of treatment, and interpretation of results.

RESULTS

A total of 16 reports deal with randomized controlled studies addressing aspects of surgical procedures or devices in the treatment of epilepsy, or with aspects of management of medical issues in relation to surgical interventions. Of these, twelve are

actual reports of surgical RCTs, two are reports of failed surgical RCT attempts, and two are RCTs of medical perioperative care.

Early Attempts at Surgical RCTs

Two of the studies are descriptions of early, unsuccessful attempts at randomized trials of resective brain surgery for epilepsy.^{7,8} As early as 1963, Ommaya⁸ described in abstract form the results of temporal lobectomy in 106 patients and craniotomy without lobectomy in 25 patients in whom intraoperative electrocorticography led to the decision not to resect brain tissue. The results were strikingly similar in both groups. Substantial improvement occurred in 55% of patients with resections and in 59% of those without resections. Furthermore, those without resection had "better adjustment." Ommaya goes on to propose that this justifies performing a controlled clinical trial, which never took place. In the second report, Dasheiff et al⁷ describe their unsuccessful attempt at implementing an initially funded RCT of temporal lobe epilepsy surgery in Pittsburgh, citing as causes for failure the inability to recruit patients and to maintain funding for a slow recruiting trial.

RCT of Perioperative Care

Two studies address aspects of clinical management directly related to epilepsy surgery.^{9,10} In 1992, Kuzniecky et al⁹ reported a small randomized trial of 40 patients who, following temporal lobectomy, were allocated to treatment with carbamazepine alone, or continuation with anticonvulsant polytherapy. After one year, no significant differences were observed in the number or types of seizures, but more patients experienced side effects in the polytherapy group (30%) than in the monotherapy group (10%). In the second study, Sahjpal et al¹⁰ compared dexamethasone versus placebo to treat pain, nausea and systemic symptoms in patients following subdural electrode implantation. They found a trend towards improvement in pain, nausea, and meningismus as well as lower temperature in those receiving dexamethasone for 72 hours. However, the results were not statistically significant.

RCTs of Vagus Nerve Stimulation

The remaining 12 studies tested actual surgical interventions or surgical devices in a randomized controlled fashion (Table 1). Five of these assessed the efficacy of vagus nerve stimulation in 416 patients with refractory partial seizures with or without secondary generalization.¹¹⁻¹⁷ Three studies tested low versus high intensity stimulation^{11,13,14,17} one tested fast versus slow stimulation algorithms,¹² and one assessed three different duty cycles.¹⁶ All studies had a short duration of follow-up not exceeding three months (Tables 1 and 2).

RCTs of Deep Brain Stimulation

Three studies have evaluated the effect of electrical brain stimulation in patients with refractory epilepsy¹⁸⁻²⁰ (Table 1). One study, describes randomized trials in four individual patients (n-of-1) undergoing unilateral hippocampal stimulation, which was turned on and off at random in three treatment pairs.²⁰ Although not significant, the results suggested a beneficial trend

Table 1: Surgical Randomized Trials in Epilepsy - 12 Studies Involving 662 Patients

	Seizure Type	N	Comparison	Design	Time	Centre(s)	Blind
VNS							
VNS Study group, 1995 ¹⁷	Partial Seizures	114	Low vs High	Parallel	3 month	Multi	Double
Handforth, 1998 ¹³	Partial Seizures	196	Low vs High	Parallel	3 month	Multi	Double
Amar, 1998 ¹¹	Partial Seizures	17	Low vs High	Parallel	3 month	Single	Double
Scherrmann, 2001 ¹²	Mixed	28	Fast vs Slow	Parallel	?	Single	No
DeGiorgio, 2005 ¹⁶	Partial Seizures	61	Three duty cycles	Parallel	3 month	Multi	No
Brain Stimulation							
Fisher, 1992 ¹⁸ (Thalamic)	GTC	7	ON vs OFF	Cross-over	3 month	Single	Double
Velasco, 2005 ¹⁹ (Cerebellar)	GTC	5	ON vs OFF	Parallel	3 month	Single	Double
Téllez-Zenteno, 2006 ²⁰ (Hippocampal)	TLE	4	ON vs OFF	Cross-over	6 month	Single	Double
Surgical Techniques							
Wyler, 1995 ²¹ (Hippocampal resection)	TLE	70	Small vs Large	Parallel	1 year	Single	Single
Hermann, 1999 ²² (Superior temporal gyrus)	TLE	30	Resection vs Preservation	Parallel	8 month	Single	Single
Lutz, 2004 ²³ (Selective AH)	TLE	80	Transsylvian vs Transcortical	Parallel	1 year	Single	No
Surgical vs Medical							
Wiebe, 2001 ²⁴ (Temporal lobectomy)	TLE	80	Resection vs Medical Therapy	Parallel	1 year	Single	Single

VNS-vagus nerve stimulation, GTC-generalized tonic clonic, TLE-temporal lobe epilepsy, AH-amygdalohippocampectomy

with hippocampal stimulation, and no adverse effect on memory or cognitive function. Another study reports the results of a pilot analysis of bilateral centro-median thalamic stimulation in seven patients in a randomized, three-month crossover, double-blind, controlled study involving patients with generalized seizures.¹⁸ No significant differences were found in seizure control during the randomized controlled phase, but three patients experienced a 50% reduction in seizure frequency. In the third study, Velasco et al¹⁹ report the results of a pilot analysis of bilateral cerebellar superomedial electrical stimulation in five patients with medically refractory generalized tonic clonic seizures, randomized to stimulator on (n=3) or stimulator off (n=2). Seizures were reduced to 33% of baseline frequency with stimulation, as compared to no seizure reduction in those without stimulation. Unblinded stimulation for 24 months in some patients showed continued benefit. Electrodes had to be removed in one patient because of an infection (Table 2).

RCTs Comparing Surgical Approaches

Of the five remaining studies, four compare different surgical resective techniques (Table 1). Wyler et al²¹ randomized 70 patients to partial hippocampectomy to the level of the cerebral peduncle or to total hippocampectomy to the level of the superior colliculus. Seizure freedom was achieved by 69% of patients

with total versus 38% of patients with partial hippocampectomy, with no difference in neuropsychological function. Hermann et al²² evaluated visual confrontation naming in 30 patients with temporal lobe epilepsy randomized to resection versus sparing of the superior temporal gyrus. No difference in language function between the two procedures was found. In the third study, Lutz et al²³ evaluated neuropsychological function in 80 patients with temporal lobe epilepsy who were randomized to receive selective amygdalohippocampectomy by the transsylvian (41 patients) or the transcortical approach (39 patients). No differences were found at six months or one year in seizure freedom (75% each group) or neuropsychological function, with the exception of improved phonemic fluency with the transcortical approach.

RCTs of Medical vs Surgical Therapy

Only one study has compared the efficacy and safety of temporal lobe resection versus medical therapy. Wiebe et al²⁴ randomized 80 patients with temporal lobe epilepsy to anterior temporal lobectomy versus optimum medical treatment using a parallel group, RCT with masked outcome assessment at one year. In an intention to treat analysis, the cumulative proportion of patients who were free of disabling seizures was 58% in the surgical group and 8% in the medical group (Table 2). Quality of

Table 2: Surgical Randomized Trials in Epilepsy - Outcomes

	Number of Patients	Main Outcome	Main Results (%)	Other Outcomes
VNS				
VNS Study Group, 1995 ¹⁷	114	50% sz reduction	31 high/18 low	NNT=6 One myocardial infarction
Handforth, 1998 ¹³	196	50% sz reduction	23 high/16 low	NNT=14 Better global outcome, no complications
Amar, 1998 ¹¹	17	Mean % sz reduction	71 high/6 low	- No complications
Scherrmann, 2001 ¹²	28	50% sz reduction	No differences	NS -
DeGiorgio, 2005 ¹⁶	61	50% sz reduction	No differences	NS One patient with vocal cord paralysis
Brain Stimulation				
Fisher, 1992 ¹⁸ (Thalamic)	7	Mean % sz reduction	30% ON/8% OFF	NS Intense stimulation induced SW
Velasco, 2005 ¹⁹ (Cerebellar)	5	Mean % sz reduction	67% ON/7% OFF	p=0.02 Infection & removal in 1 patient
Tellez-Zenteno, 2006 ²⁰ (Hippocampal)	4	Median % sz reduction	26% ON/46% worse OFF	NS No cognitive changes
Surgical Techniques				
Wyler, 1995 ²¹ (Hippocampal resection)	70	% sz free	69% large/38% small	NNT=4 No cognitive effects
Hermann, 1999 ²² (Superior temporal gyrus)	30	Language function	No differences	NS Older age predicted speech dysfunction
Lutz, 2004 ²³ (Selective AH)	80	Cognitive function	No differences	NS Fluency worse with Transsylvian
Surgical vs Medical				
Weibe, 2001 ²⁴ (Temporal lobectomy)	80	% sz free	58% surgery/8% medical	NNT=2 Surgery had better QOL, but 10% complication rate. One death in medical group

VNS – vagus nerve stimulation, sz – seizure, NS – not significant, NNT – number needed to treat, SW – spike wave, AH – selective amygdalohippocampectomy, QOL – quality of life

life was superior in the surgical group, 10% of patients had surgical adverse effects, and one patient died in the medical group. Finally, Engel et al²⁵ recently initiated a study randomizing patients with early intractable temporal lobe epilepsy to surgical or medical therapy. Recruitment to this multicenter trial has been problematic and has resulted in discontinuation of the study.

WHERE DO WE GO NEXT?

Randomized controlled trials are unquestionably the gold standard to test new interventions, but such trials remain difficult to perform when evaluating epilepsy surgical techniques, and single centres are unable to undertake timely RCTs with adequate sample sizes. A glance at efforts in this area during the last decade identifies few successes and also some casualties.⁷ Most recently, the NIH-funded, multicentre ERSET study (Early Randomized Surgical Epilepsy Trial) was stopped because of

unacceptably low enrollment rates.²⁵ To avoid the treacherous road of the epilepsy surgery RCT, other researchers have opted for non-randomized, non-controlled prospective designs.²⁶ We suggest that for high quality epilepsy surgery research to move forward the following aspects need to be addressed.

Early identification of surgical candidates

Surgical superiority has been demonstrated for chronically pharmacoresistant patients suffering from temporal lobe epilepsy through an RCT,²⁴ and the American Academy of Neurology's has crystallized this into clinical practice guidelines.³ However, no surgical RCTs have been performed in extratemporal lobe epilepsy or early after diagnosis of localization related epilepsy. Experience with unsuccessful attempts at early surgery RCTs has taught us that knowledge about the course of illness of various surgically amenable epilepsies would go a long way towards defining eligibility criteria for enrolling patients in surgical

RCTs. Time to intractability, severity of epilepsy and identification of early predictors of pharmacoresistance play a defining role in planning and executing surgical epilepsy RCTs. Although reports of surgical cohorts often document a lag of more than 20 years between epilepsy diagnosis and surgical intervention,^{24,27} it has become clear that not all patients remain medically refractory during this entire period. In a multicentre adult surgical cohort, Berg et al²⁸ reported a median latency of nine years from diagnosis of epilepsy to intractability (failure of >2 antiepileptic drugs). Conceivably, patients and clinicians would not consider epilepsy surgery as long as there is a reasonable response to medications. Questions about which patients become medically refractory, at what point in time and what impact epilepsy has on their physical and psychosocial function need to be explored to allow for adequate RCT planning and implementation. A better understanding of patients' and clinicians' attitudes and knowledge regarding epilepsy surgery is equally important. For example, even after a surgical RCT proved conclusively that surgery was superior to medical therapy, some clinicians expressed a staunch view that surgery was barbaric and unwarranted.¹⁵ Evidently, knowledge transfer and education are important in the referral process of patients to epilepsy surgery centres.

Building the research infrastructure

A network of epilepsy surgery centres that collaborate to collectively design and implement surgical RCTs is essential. Not only would this allow for the faster recruitment of sufficient numbers of patients, but it would also serve other important research functions. The concept is not novel and has yielded spectacular results in other areas. Consider the example of the Canadian Critical Care Trials Group (CCCTG).²⁹ This non-profit organization not only fosters, but actively develops and implements investigator initiated trials. With a solid history of success, the CCCTG has a simple structure, consisting of a chair, and executive and administrative committees, with a broad mix of members, whose function is to provide scientific and administrative support to the membership, and aid in grant and manuscript preparation. Members contribute a modest fee which helps support the organization. Any CCCTG member can develop protocols throughout the year. Draft protocols are circulated to the membership prior to review in biannual meetings. Detailed discussions at meetings involve aspects of relevance, methodology, implementation, statistics and ethics, all of which lead to iterative protocol refinement. Each protocol is voted for membership in the CCCTG and if accepted, undergoes further internal peer-review, prior to submitting for external peer-reviewed funding.²⁹ Moreover, this research network can also assist in organizing research projects aimed at answering questions about risk factors, which typically require cohort-based studies,³⁰ and it can assist in developing quality improvement tools for monitoring patient participation in RCTs.³¹ Groups such as the CCCTG typically develop and adhere to policies regarding study management methods, ethics and authorship.²⁹ By fulfilling these functions, and working within existing Canadian epilepsy organizations, a "Canadian Epilepsy Surgery Study Group" (CESSG) could become a strong vehicle for epilepsy surgery research.

Establishing research priorities

The broad range of research questions involving epilepsy surgery requires different study designs. For interventions, RCTs are the ideal vehicle, whereas exploration of risk factors, determinants of prognosis, and analyses of diagnostic accuracy require adequately designed cohort studies. Accordingly, the exploration of different clinical questions entails a gradient of clinical importance and also gradations of feasibility and ease of implementation. Prioritizing research efforts ensures that high-yield, feasible studies move forward, and it also increases the likelihood of obtaining peer-reviewed funding. As epilepsy surgery research agendas evolve, more wide-ranging prioritizing strategies may become necessary. For example, consensus methods have been used successfully to establish national research priorities in critical care in the United Kingdom.³² One of the main functions of an epilepsy surgery study group would be to prioritize research initiatives brought forward by its membership, and to help refine initial ideas into mature protocols with higher impact and likelihood of implementation. An example of epilepsy surgery research areas, categorized in terms of their expected complexity and feasibility is given in Table 3.

A Canadian Epilepsy Surgery Study Group makes sense

The portability, relative homogeneity and universality of the Canadian health care system permit an easier organization of homogeneous research groups than is possible in for profit or mixed health care systems. Patients with epilepsy in Canada can receive a high level of epilepsy care in their own province or by referral to specialized centres in other provinces. The Canadian community of clinicians specializing in epilepsy and epilepsy surgery is relatively small and follows well known practice patterns. A 2004 Canadian survey of epilepsy resources revealed that 74 neurologists (provincial range 0 to 22, median 8) and 23 neurosurgeons (provincial range 0-6, median 4) focus their practice on epilepsy. Although numbers change rapidly, there are approximately 20 epilepsy centres in Canada involved in presurgical evaluation and epilepsy surgery (median 3 per province). Although the availability of sophisticated technology such as radiosurgery, stereotactic and functional surgery, magnetoencephalography (MEG), positron emission tomography (PET) scanning and fMRI varies from centre to centre, standard diagnostic and surgical tools are common to all centres, and relative homogeneity of epilepsy care exists across the country. Finally, one cannot overemphasize the importance of a strong tradition in epilepsy surgery research in Canada, which provides a firm foundation for ongoing and future research initiatives. Consider for example, that after the United States, Canada contributes the largest number of manuscripts to *Epilepsia*, the world's flagship journal for epilepsy related publications (personal communication, editorial board). If significant interest exists in establishing a trials network through a Canadian Epilepsy Surgery Study Group exists in the epilepsy community, reasonable next steps would be to assemble a task force to work out a specific roadmap, to launch the study group in the context of specific research protocols, and to make certain that the study group works in concert with existing Canadian epilepsy research efforts.

In conclusion, our analysis confirms that RCTs in the field of epilepsy surgery are rare, yet critical in determining optimal care

Table 3: Sample research topics amenable to multicentre studies in Canada, and expected level of implementation difficulty

Example of Research Topic	Expected level of study difficulty (low, medium, high)*
Continuous versus sample EEG reading in select persurgical cases	Low
Role of Ambulatory EEG in select presurgical cases	Low
Use of antiepileptic drugs post-surgery	Low
Role of various symptomatic treatments for patients undergoing intracranial monitoring	Low
Role of alternative therapies for symptom control or for seizure control for those not deemed to be surgical candidates	Medium
Prolonged outpatient versus continuous inpatient recordings in TLE patients	Medium
Comparison of surgical techniques for specific clinical entities	Medium
Role of various neuroimaging techniques	Medium
Role of brain stimulation for various epilepsies	Medium-High
Role of intracranial monitoring in uncertain cases	Medium-High
Role of structured psychosocial intervention in improving surgical outcomes	Medium-High
Role of new surgical techniques (gamma knife, stereotactic ablation, etc.)	Medium-High
Selective amygdalohippocampectomy vs anterior temporal lobectomy	High
Medical vs surgical therapy for extratemporal epilepsy	High
Role of surgery for specific structural abnormalities	High

* Level of difficulty is based on expected sample size requirements and logistic aspects.

for patients with pharmacoresistant epilepsy. We also highlight the importance of approaching epilepsy surgery research collectively in Canada. This would allow addressing crucial unanswered questions, such as understanding the course of illness of various forms of epilepsy, predicting pharmacoresistance, identifying surgical candidates early on, and performing adequately sized surgical RCTs. Ability and opportunity exist to move forward. Establishing a trials network through a Canadian Epilepsy Surgery Study Group would enable future collaborative multicentre research efforts and allow the pursuit of high quality, sustainable research in epilepsy surgery.

REFERENCES

- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995; 273: 408-12.
- Brown S, Thorpe H, Hawkins K, Brown J. Minimization--reducing predictability for multi-centre trials whilst retaining balance within centre. *Stat Med*. 2005; 24: 3715-27.
- Engel J, Jr., Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology*. 2003; 60: 538-47.
- Wiebe S. Randomized controlled trials of epilepsy surgery. *Epilepsia*. 2003; 44 Suppl 7:38-43.
- Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med*. 2001; 344: 710-9.
- Dekkers W, Boer G. Sham neurosurgery in patients with Parkinson's disease: is it morally acceptable? *J Med Ethics*. 2001; 27: 151-6.
- Dasheiff RM, Ryan CW, Lave JR. Epilepsy brain surgery: a Pittsburgh perspective. *Seizure*. 1994; 3: 197-207.
- Ommaya AK. Behaviour after temporal lobectomy. *J Neurol Neurosurg Psychiatry*. 1963; 26: 556(Abstract)
- Kuzniecky R, Rubin ZK, Faught E, Morawetz R. Antiepileptic drug treatment after temporal lobe epilepsy surgery: a randomized study comparing carbamazepine and polytherapy. *Epilepsia*. 1992; 33(5): 908-12.
- Sahjpal RL, Mahon J, Wiebe S. Dexamethasone for morbidity after subdural electrode insertion--a randomized controlled trial. *Can J Neurol Sci*. 2003; 30: 340-8.
- Amar AP, Heck CN, Levy ML, Smith T, DeGiorgio CM, Oviedo S, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. *Neurosurgery*. 1998; 43: 1265-76.
- Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. *J Clin Neurophysiol*. 2001; 18: 408-14.
- Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998; 51: 48-55.
- A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*. 1995; 45: 224-30.
- Richards TA. Surgery for temporal lobe epilepsy. Letter to the editor. *N Engl J Med*. 2002; 346: 293(Abstract)
- DeGiorgio C, Heck C, Bunch S, Britton J, Green P, Lancman M, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology*. 2005; 65: 317-9.
- The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology*. 1995; 45: 224-30.
- Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia*. 1992; 33: 841-51.
- Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. *Epilepsia*. 2005; 46: 1071-81.
- Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology*. 2006; 66:(Abstract)
- Wyller AR, Hermann BP, Somes G. Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery*. 1995; 37: 982-90.

22. Hermann B, Davies K, Foley K, Bell B. Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: a randomized prospective clinical trial. *Epilepsia*. 1999; 40: 1070-6.
23. Lutz MT, Clusmann H, Elger CE, Schramm J, Helmstaedter C. Neuropsychological outcome after selective amygdalo-hippocampectomy with transylvian versus transcortical approach: a randomized prospective clinical trial of surgery for temporal lobe epilepsy. *Epilepsia*. 2004; 45: 809-16.
24. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001; 345: 311-8.
25. Engel J, Jr. The timing of surgical intervention for mesial temporal lobe epilepsy: a plan for a randomized clinical trial. *Arch Neurol*. 1999; 56: 1338-41.
26. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, et al. Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology*. 2003; 61: 1680-5.
27. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology*. 2005; 65: 912-8.
28. Berg AT, Langfitt J, Shinnar S, Vickray BG, Sperling MR, Walczak T, et al. How long does it take for partial epilepsy to become intractable? *Neurology*. 2003; 60: 186-90.
29. Cook D, Brower R, Cooper J, Brochard L, Vincent JL. Multicenter clinical research in adult critical care. *Crit Care Med*. 2002; 30: 1636-43.
30. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med*. 1999; 27: 2812-7.
31. Foster D, Cook D, Granton J, Steinberg M, Marshall J. Use of a screen log to audit patient recruitment into multiple randomized trials in the intensive care unit. Canadian Critical Care Trials Group. *Crit Care Med*. 2000; 28: 867-71.
32. Vella K, Goldfrad C, Rowan K, Bion J, Black N. Use of consensus development to establish national research priorities in critical care. *Br Med J*. 2000; 320: 976-80.