Chapter 5. Future Research

In this section, we first discuss particular shortcomings of study design and research in the available literature. Then we focus on the most important areas needing research and discuss the optimal designs of trials that would answer these outstanding questions.

Shortcomings of Available Research

Our analysis suggests that at least some patients receiving treatment for epilepsy either do not have epilepsy or have another condition in addition to epilepsy that also causes seizures or seizure-like events. The extent to which this phenomenon affects interpretation of the current literature is unclear. Studies that clearly describe the diagnostic procedures used to confirm that patients actually have epilepsy are needed and would present a more accurate assessment of the efficacy of the treatment under study.

Our analysis also suggests that some patients receive AEDs at less than the maximum tolerable dose. Future studies could ensure that their patients are truly treatment-resistant by enrolling only patients who are optimized and compliant with their current therapy.

There are many uncontrolled studies of epilepsy treatments. In the absence of a control group, the effects of treatment cannot be differentiated from placebo effects, regression to the mean, extraneous events, or other threats to internal validity. Although there are situations in which controlled trials are impractical (e.g., once a patient is determined to be a candidate for surgery withholding treatment may be considered unethical), controlled trials are needed to provide a more accurate picture of the effects of treatment.

Studies with inadequate numbers of patients cannot detect clinically meaningful differences in outcomes between treatment groups. When designing clinical trials, *a priori* power analysis calculations can be used as a guide to ensure that sufficient numbers of patients are enrolled so that the proposed trial can uncover clinically meaningful relationships between treatments and outcomes.

Many publications do not contain sufficient information to enable the reader to accurately judge the evidence. Reports on the effect of treatment on seizure frequency seldom gave sufficient data on pre- and posttreatment seizure frequency. Further, commonly reported outcomes do not capture information from patients who do not improve after treatment. Some confusion could be alleviated if seizure-free outcome measurements were standardized. A well-reported trial would include seizure frequency as well as a measure of data dispersion, both at baseline and at several followup periods.

Optimal Study Designs

Studies of diagnostics

The lack of an accepted gold standard for the differential diagnosis of epileptic seizures from nonepileptic seizures makes evaluating the utility of any given diagnostic problematic. This is because of the difficulty in verifying that the diagnostic decisions that result from the use of the test are correct. Given this lack of an acceptable gold standard, attempting to determine whether the use of a diagnostic improves patient outcomes may offer a fruitful avenue for future research.

Such an approach requires determining whether the use of the diagnostic of interest ultimately leads to improved patient outcomes. Because the findings of the diagnostic of interest will likely influence, but not dictate, medical management, the true strength of the relationship between the use of the diagnostic and patient outcome is difficult to determine.[42] As a consequence, determining whether use of a diagnostic improves patient outcomes requires a prospective, randomized controlled trial. For example, a study designed to examine the effectiveness of video-EEG in differentiating epileptic from nonepileptic seizures might randomize patients to receive a differential diagnosis using either video-EEG alone, or some standard diagnostic regimen. After a reasonable followup period, outcomes in all patients would be measured.

Because a diagnosis of epilepsy is not made based on the findings of a single diagnostic technology, another fruitful avenue for future research would be to evaluate the effectiveness of different clinical algorithms that utilize data collected from combinations of diagnostic technologies. Because of the lack of a gold-standard (hence the need for clinical algorithms), this path, like the assessment of an individual diagnostic, may also be best approached by attempting to determine whether the use of different diagnostic algorithm improves patient outcomes. Again, this approach would require a prospective, randomized controlled trial.

Studies of treatment

Prospective, randomized double-blinded controlled trials are widely considered to provide the highest quality of evidence for treatment effectiveness. Nonrandomized trials may have differences in outcomes between patient groups because of differences in the characteristics of the patient groups, rather than the treatment applied. Trials without a control group are unable to examine the potential for recovery in the absence of treatment, and they do not allow an accurate gauge of the magnitude of any change that occurs after treatment. Blinding of patients and evaluators to treatments avoids the potential for placebo effects and previously held beliefs about the effectiveness of treatments to impact on the results of trials.

In the literature on drug strategies, an important direction for future research involves direct comparisons between the drug strategies for treatment-resistant epilepsy. None of the studies included in our assessment of drug strategies made direct comparisons between sequential monotherapy and polytherapy. Ideally, a trial would randomize patients to different drug strategies, and compare seizure frequency outcomes as well as adverse effects of treatment.

Another area for future research on drugs concerns the adverse effects patients experience from their pretrial drug regimens. The switch to a new drug (sequential monotherapy) or the addition of a new drug (polytherapy) may reduce these pretrial adverse effects, or potentially may exacerbate them. Changes in the frequency and severity of the adverse effects associated with each drug treatment strategy need to be evaluated because patients and clinicians seek to reduce adverse effects as well as seizure frequency.

Prospective studies of surgical interventions are needed. This approach would allow seizure and nonseizure-related outcome measures to be recorded at multiple followup periods (1 year, 2 year, 5 year, etc.) rather than the single mean or median followup reported in most retrospective studies. Better reporting of patient characteristics are needed, including not only patient age but age at first seizure, duration of epilepsy, pathology, gender, and baseline seizure frequency. If possible, individual patient characteristics could be reported to facilitate pooling and analysis of data across studies when study sizes are small (less than 20 patients). Studies reporting standardized quality of life measures, validated for patients with epilepsy, would help in determining the effect of surgery on this important nonseizure-related outcome. Studies reporting other types of nonseizure-related outcome measures, such as employment, education,

and cognitive function data, are also needed. Additional suggestions for standardized outcome reporting in studies of epilepsy surgery are discussed in Wieser, Blume, Fish, et al.[381]

Higher quality controlled trials are particularly lacking for the nonmedical treatments such as education and training in skills that may help prevent seizures or enable patients to better adapt to seizures. This area constitutes another important direction for future research.

Studies of patient characteristics related to employment and school

Reporting of employment and schooling status among patients with treatment-resistant epilepsy is particularly lacking in both the medical and nonmedical treatment literature. Few treatment studies considered employment and schooling as important outcomes and therefore an evidence-base for relating patient characteristics to employment and schooling is missing.

The ideal study design to address this question would be a prospective cohort study using multiple regression techniques to evaluate the potential correlation between specific patient characteristics and the ability to work or attend school both before and after treatment. This is an area in particular need of future research and higher quality studies.

Studies of mortality

The present literature has a number of large (mostly retrospective) studies that have calculated SMRs for overall mortality, but few studies have calculated separate SMRs for specific causes of death or specific age subgroups. To generate meaningful data, cohort studies must enroll sufficient numbers of patients and follow the patients for sufficient periods. The most useful study of mortality among patients with treatment-resistant epilepsy would be a large prospective study that followed patients for several years. In addition to calculating an SMR for overall mortality, the study would calculate SMRs for specific causes of death, especially those that could be related to epilepsy (such as accidents, drowning, and motor vehicle accidents). At this time, no published study of treatment-resistant patients has presented SMRs for these causes of death. Future studies would ideally present SMRs for different age subgroups within the larger study population. The United Kingdom National General Practice Study of Epilepsy, which has prospectively followed several hundred newly-diagnosed patients for over a decade,[365] provides a good model for a future study of mortality among patients with treatment-resistant epilepsy.

Large prospective studies where all suspected SUDEP cases receive an autopsy are needed. An autopsy is particularly important because it provides the best evidence that the death did not have an explainable cause. This would increase the accuracy of estimates of SUDEP rates for different age subgroups of patients with treatment-resistant epilepsy.

More prospective case-control studies using multiple regression analysis would be useful to address the potential relationship between SUDEP and seizure type or frequency. We found only two large studies using multiple regression that have thus far addressed this question. Future studies would ideally include a hundred patients or more to ensure that there is adequate statistical power to detect correlations. Multiple regression analysis is needed to reduce the effect of possible confounding variables and increase the likelihood that an observed statistically significant correlation represents an actual causal relationship.