Chapter 4. Conclusions

Definition of Treatment-Resistant Epilepsy

Treatment resistance is infrequently defined in the literature. Less than one third of the publications we surveyed reported any definition of this term. Common components of the definitions found in those studies giving a definition included the number of drugs a patient tried before being considered treatment-resistant and whether these drugs were administered to the maximum tolerated dose. Seizure frequency and duration of illness were also included in some definitions. However, no single characteristic was reported by a majority of studies, clinical guidelines, or review articles.

With few explicit definitions available in the studies of patients with treatment-resistant epilepsy, we examined the inclusion and exclusion criteria of these studies for implicit definitions. Although no clear consensus could be discerned, some differences between types of studies were observed. Drug trials tended to require fewer failures of drug treatment than surgical trials. This is probably a result of the nature of surgical trials rather than a true difference of opinion on the definition of treatment resistance. A patient with seizures resistant to one drug is simply given another drug. In contrast, before surgery is considered, a patient must undergo a thorough assessment of potentially effective drug regiments. Implied definitions of treatment resistance are thus situational rather than absolute.

Many studies required a minimum baseline seizure frequency (several seizures per month) before the patient could be accepted into a study. This minimum may be a function of trial design and statistical power rather than a part of the definition of treatment resistance. Requiring a higher baseline seizure frequency makes demonstrating a statistically significant reduction in frequency easier. This does not explain why studies of pediatric patients tended to require lower seizure frequencies than studies that did not examine a special patient group. The reason for this difference in requirements is unclear. In practice, the effect of seizures on the patients' daily lives may be more important than their absolute frequency.

Despite the fact that terms such as "intractable", "refractory" or " treatment-resistant" appear regularly in the published literature, no consensus exists as to precisely what these terms mean.

Rediagnosing and Re-evaluating Treatment-Resistant Epilepsy

We addressed this question by partitioning it into four separate subquestions. The first two subquestions address the differential diagnosis of epileptic seizures from nonepileptic seizures. The remaining two subquestions address the differential diagnosis of different seizures types. Whether we addressed some questions depended on the findings from previous questions.

Do all patients with treatment-resistant epilepsy truly have epilpesy?

Evidence from five studies demonstrates that some patients originally thought to have treatment-resistant epilepsy do not have epilepsy at all, or had a combination of both epileptic and nonepileptic seizures.

Precise estimation of the proportion of such patients in the population of patients with a diagnosis of treatment-resistant epilepsy is not possible. This was because all relevant prevalence data currently come from two distinct groups of adult patients with treatment-resistant epilepsy. The first of these groups is comprised of patients referred to specialist epilepsy or neurophysiology centers for evaluation of their seizures, and the second is comprised of surgical candidates. No data on misdiagnosis among pediatric populations with treatment resistant epilepsy was identified.

Data from four of the five above-noted studies suggest that the prevalence of nonepileptic seizures in patients referred for evaluation is approximately 35 percent. This figure, however, likely overestimates the true proportion of patients with nonepileptic seizures among patients thought to have epilepsy, since some of the patients referred for specialist evaluation are sent because of a suspicion that these patients' seizures were not epileptic. Data from the single study of surgical candidates suggest that, while no patients were found to suffer from nonepileptic seizures alone, about 8 percent suffered from a combination of epileptic and nonepileptic seizures. Because all five of the included studies consisted solely of adult patients, it is unclear whether these data are generalizable to pediatric populations.

These findings mean that some of the patients described in articles included in this Evidence Report may not have epilepsy. If this is the case, then our estimates of the efficacy of the interventions that we address may be imprecise. This is because an effective intervention for epilepsy may not work on patients who do not truly have epileptic seizures. Conversely, nonepileptic seizures, in particular psychogenic seizures, may be more susceptible to a placebo effect compared to true epileptic seizures.

Which diagnostic modalities differentiate seizure types mistaken for epilepsy?

We next evaluated the available evidence to determine the ability of fourteen diagnostics modalities to differentiate epileptic seizures from nonepileptic seizures. Only measurement of blood prolactin levels was addressed by a sufficient number of studies to be included in this report.

Our assessment of study quality suggest that definitive conclusions cannot be draw about whether blood prolactin level measurements have a useful role in differentiating epileptic seizures from nonepileptic seizures. Acknowledging this, the results of our analysis suggest that blood prolactin levels, measured within 60 minutes of seizure onset, are potentially useful in distinguishing syncopal or psychogenic seizures from complex partial seizures. However, the test appears to be of no little or no value in discriminating simple partial seizures from psychogenic or syncopal seizures.

Is seizure type misdiagnosed in patients with treatment-resistant epilepsy?

Currently, there are insufficient published data available to answer this question.

Which diagnostic modalities differentiating seizure types?

This question was not addressed because insufficient published data were available to determine if seizure type was misdiagnosed in patients with treatment-resistant epilepsy. This question could only be answered if seizure type was misdiagnosed in patients with treatment-resistant epilepsy.

Optimization of Antiepileptic Drugs

The literature demonstrates that not all patients with treatment-resistant epilepsy are optimized at their current level of AED therapy. Because our literature searches did not locate any large, population-based studies that addressed whether patients with treatment-resistant epilepsy were receiving optimized therapy, estimating the percentage of nonoptomized patients is not possible. In most studies, the degree to which patients were noncompliant with their prescribed drug regimen could not be determined. Regardless, the evidence suggests that some patients reported to be treatment-resistant may not actually be treatment-resistant. This has implications when clinicians are considering changes in a patient's current AED therapy or referring patients for surgical evaluation.

Drug Treatment Strategies

We examined three drug treatment options for patients with treatment-resistant epilepsy: sequential monotherapy, polytherapy, and optimized current therapy. Sequential monotherapy involves the initiation of a single new drug after the removal of all previous drugs. Polytherapy involves the addition of a new drug (or drugs) to patients' prior drug regimens. Optimized current therapy involves either increasing the dosage of the current drug (or drugs) to maximum tolerable levels, modifying the frequency of dosing, or reducing the total number of drugs. As such, the choice between these treatments can be characterized as "switch to a new drug" (sequential monotherapy), "add a new drug" (polytherapy), or "adjust the current regimen" (optimized current therapy). Because published studies of a given strategy investigated the effects of specific drugs rather than general drug strategies, we aggregated the results of different studies for each strategy in order to determine the effectiveness of that strategy.

Sequential monotherapy

The clinical intent of switching patients with treatment-resistant epilepsy to a new monotherapy drug is to reduce seizures as well as side effects. To determine the efficacy of this drug strategy, the relevant control group would be a group of patients who continued to receive their prestudy drug regimens. However, none of the studies of sequential monotherapy included such a control group. Therefore, the conclusions about the effect of sequential monotherapy are based on the results of uncontrolled studies.

Meta-analytic threshold analysis indicated that during studies of sequential monotherapy, an estimated 30% of patients experienced either a doubling of monthly seizure frequency or a doubling of two-day seizure frequency. Despite the fact that these data are from studies that indirectly addressed monotherapy, three factors suggest that these increases were the result of switching patients from multiple antiepileptic drug therapy to a single drug: the use of *a priori* exit criteria, the removal of all prestudy drugs, and the anticipated effects of regression-to-the-mean.

Further meta-analyses indicated that an estimated 16% of patients were seizure-free during studies of sequential monotherapy. When only longer-term studies (followup of 16 weeks or more) were included, the estimate was 11%. However, because these data are from studies that only indirectly addressed monotherapy, they do not definitively show that sequential monotherapy actually caused any of these patients to become seizure-free. Such a definitive conclusion would require randomization of patients to either sequential monotherapy or a

continuation of the prestudy drug regimen. When the seizure freedom percentages (11%-16%) are considered together with the percentage of harmful increases in seizures (30%), sequential monotherapy appears more likely to be harmful than beneficial.

No studies compared the adverse effects experienced by patients during sequential monotherapy with the adverse effects they had been experiencing during their prestudy drug regimens. Many patients (53% to 95%) experienced mild adverse effects to the new monotherapy drug. An estimated 5% of patients exited trials of sequential monotherapy due to adverse effects. There was insufficient evidence to draw firm conclusions about the influence of sequential monotherapy on quality of life, mood, cognitive function, ability to return to work, ability to return to school, ability to hold a driver's license, or mortality.

Polytherapy

As with sequential monotherapy, the clinical intent of adding a drug (or drugs) to patients' regimens is to reduce both seizures and side effects. The evidence base for this drug treatment strategy was of generally high quality because all trials were randomized, placebo-controlled, and double-blinded. Each trial investigated the effectiveness of a specific add-on drug, and we aggregated the trials' results to assess the effectiveness of the polytherapy strategy. This aggregation has limited generalizability because each trial employed different add-on designs, and the effect of a new AED may depend on the other AEDs in patients' regimens. Our meta-analytic summary estimates can only approximate the typical effect of adding a new drug to patients' prior AED regimens. The actual effect in any single patient is likely to depend on the specific AED to be added as well as characteristics of AEDs already in use.

Our findings suggest that adding certain AEDs to a patient's drug regimen has potential advantages and disadvantages. Patients who receive these add-on drugs are more likely to experience reductions in seizures compared to patients who receive an add-on placebo. This benefit is evident from several different measures of seizure frequency, including the percentage of patients who experienced 50% reduction (35% in add-on drug groups vs. 13% in add-on placebo groups).

However, recipients of these add-on drugs are more likely to experience adverse effects leading to trial exit compared to placebo recipients (8% vs. 4%, respectively). Taken with the findings on seizure frequency, polytherapy appears to involve a tradeoff: adding a drug can reduce seizures, but it can also cause more side effects. However, many more patients are likely to experience benefit than harm. There was insufficient evidence to draw firm conclusions about the influence of polytherapy on quality of life, mood, cognitive function, ability to return to work, ability to return to school, ability to hold a driver's license, or mortality.

Optimization of current drug therapy

We identified published articles describing studies of three different strategies designed to optimize current drug therapy. These were increasing the dosage of the current drug (or drugs) to maximum tolerable levels, modifying the frequency of dosing, and reducing the total number of drugs. Only one of these drug optimization strategies, drug reduction, was addressed by more than five studies. Thus, we did not evaluate the available data on studies of maximal tolerable dose or frequency of dosing. Therefore, our conclusions pertain solely to the implementation of the drug reduction strategy for optimization of current drug therapy.

Data from three nonrandomized controlled trials and four case series studies suggest that drug reduction may lead to increases in seizure frequency in at least some patients. Although some patients in the studies experienced reduced seizure frequency, these reductions were likely

due to regression to the mean. The only other explanation is that the withdrawn drugs were somehow causing seizures. Given that the patients included in these studies had been on their baseline AED regimens for some time, this seems implausible.

At the same time, there was little convincing evidence that drug reduction improves quality of life, mood, cognitive function, or that it reduces the occurrence of drug related adverse events. Thus, the available evidence suggests that implementation of the drug-reduction strategy may harm some patients because seizure frequency may increase and there is no evidence for any benefits. Because these conclusions are drawn from a semi-quantitative analysis of data from a small number of potentially biased studies, additional data are necessary before firm evidence-based conclusions can be drawn. Only well-designed randomized controlled trials can definitively determine whether drug optimization is effective.

We also note that these conclusions are based on our assumption that all of the patients included in the studies used to address this question truly had treatment-resistant epilepsy. If a sizable proportion of these patients were misdiagnosed (see Question 2), or were poorly optimized (see Question 3), these conclusions could be altered.

Comparisons of drug strategies

None of the included trials directly compared the drug strategies. The drug reduction strategy cannot be compared with the other two strategies, because of the differing intentions of investigators in these latter trials. Further, patients in trials of polytherapy had been receiving more drugs before the trial than patients in studies of sequential monotherapy, which also precludes directly comparing the benefits and harms of these two strategies. However, the evidence indicated that sequential monotherapy was more likely to be harmful than beneficial. By contrast, the reverse was true for polytherapy. These qualitative differences lead to the conclusion that polytherapy is preferable to sequential monotherapy for patients with treatment-resistant epilepsy.

Surgical Interventions

Our assessment of the efficacy of surgical interventions for treatment-resistant epilepsy was based on the number of patients who experienced some form of seizure freedom, reduction in overall seizure frequency, or reduction the in frequency of a specific seizure type at least 2 years after surgery. Other outcomes considered were new cases of depression or psychosis after surgery, the number of individuals with a clinically significant increase or decrease in IQ after surgery, the number of individuals with a clinically significant change in memory capacity, employment and schooling after surgery, surgical complications, and deaths due to surgery.

Temporal lobe surgery

The evidence base for temporal lobe surgery is composed almost exclusively of retrospective case series. This design, where all patients receive surgery, is vulnerable to several biases that threaten the internal validity of the results and limit their interpretation. Although some biases may be considered implausible in these studies, patient and investigator reporting biases in postoperative seizure measurement could potentially distort our measurement of the relationship between surgery and changes in postoperative seizure frequency.

Threshold analysis of 20 studies reporting patients who were completely seizure-free after surgery (no complex or simple partial seizures) suggests that 50 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to become completely

seizure-free before temporal lobe surgery could be considered to produce no additional benefit in seizure control. Threshold analysis of 26 studies reporting patients who were free of complex partial seizures after surgery (some of these patients may still experience auras) indicates that 65 percent of similar patients not receiving surgery would have to be free of complex partial seizures before temporal lobe surgery could be considered to produce no additional benefit in seizure control. Data from a RCT of temporal lobe surgery with 1-year followup suggest that these levels of recovery in untreated patients are implausible. Among the control patients in this RCT, 2.5 percent were free of complex partial seizures and auras after 1 year with an additional 5 percent free of complex partial seizures but still experiencing auras (7.5 percent total free of complex partial seizures). Therefore, our threshold analyses indicate that temporal lobe surgery is effective in producing seizure-free patients. Based on our analyses, 2 years after surgery approximately 55 percent of patients (CI: 50 percent to 60 percent) may be completely seizure-free and 68 percent of patients (CI: 65 percent to 72 percent) may be free of complex partial seizures.

Our threshold analyses also suggest that studies with different types of surgical procedures, pathologies, or countries of origin, did not affect the success of surgery as judged by the number of patients who became seizure-free. Additional analysis of individual patient data suggests that age at surgery, age of seizure onset, side of surgery, and the presence of simple partial seizures had little or no influence on seizure-free outcomes. Studies reporting gender and the presence of secondarily generalized seizures among patients with successful surgery found different results. The reason for these differences could not be explained using meta-regression.

Firm conclusions about the effect of temporal lobe surgery on employment cannot be made with the available evidence base. Only five studies reported employment data meeting the inclusion criteria for this report. Of these five studies, only three reported more than 10 patients who were working prior to surgery or not able to obtain work before surgery. There is insufficient evidence to determine the true impact of surgery on employment, other than to say that some patients were able to remain at or obtain work, while others were not able.

Although at least some surgery patients are able to remain in school after surgery, too few studies are available to make firm evidence-based conclusions on the efficacy of temporal lobe surgery based on the outcome measures assessed.

At least some patients previously unable to drive before surgery appear to be able to do so after surgery. However, because only one study reported this outcome, the generalizability of these findings are uncertain, and firm evidence-based conclusions cannot be reached.

Ten studies meeting the inclusion criteria reported new cases of depression after temporal lobe surgery. All 10 studies reported new cases of depression after surgery with a range of 4 percent to 24 percent.

Six studies meeting the inclusion criteria reported new cases of psychosis after temporal lobe surgery. Our threshold analysis of the data from these studies estimated that approximately 3 percent of surgery patients develop psychosis after surgery. However, our analysis indicates that if 2 percent of control patients developed psychosis, surgery may not be the cause of new cases of psychosis. Data from one trial with control patients suggest that this is a plausible assumption, so surgery may not be directly responsible for new cases of psychosis.

Six studies meeting the inclusion criteria reported individual changes in IQ scores after temporal lobe surgery. A clinically significant change was considered by the authors to be 1 to 2 SD. Our threshold analysis suggests that 7 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to develop a decrease in IQ before temporal

lobe surgery could be considered responsible for the decrease. A separate threshold analysis of suggests that if 10 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to develop an increase in IQ before temporal lobe surgery could be considered responsible for the increase. Mean IQ showed no appreciable change after surgery, which is consistent with the idea that roughly equal numbers of patients experience IQ increases and decreases after surgery. Data from one trial with control patients suggest that slightly less than these percentages occur in patients who do not receive surgery. Our meta-analytic threshold analysis also suggests that approximately 13 percent of patients may experience a significant increase in IQ after surgery and that approximately 10 percent of patients may experience a significant decrease in IQ after surgery. These analyses provide only an estimate of the number of patients likely to experience a significant change in IQ after surgery and do not demonstrate that surgery is directly responsible for IQ changes in these patients. Analysis of changes in mean IQ alone would not have revealed that patients were experiencing significant increases or decreases in IQ after surgery. This is consistent with the finding that approximately equal numbers of patients experience increases and decreases in IQ.

Firm conclusions about the effect of temporal lobe surgery on memory function could not be made since the five studies meeting our inclusion criteria all measured different aspects of memory function. In these studies, patients were observed with increases and decreases in memory function. While increases in memory function (range of 1 percent to 34 percent) may be attributed to surgery, the lack of control group observations in these studies prevents an actual determination of the extent to which surgery is responsible for decreases in memory function (range of 9 percent to 62 percent).

Data reported in 40 studies of temporal lobe surgery suggest that approximately 2 percent of patients may experience a serious permanent complication, usually some form of partial paralysis, after temporal lobe surgery. The rate of mild or transient complications is somewhat higher, but the exact rate is difficult to determine from available data. Data reported in 38 studies of temporal lobe surgery suggest that approximately 0.24 percent of patients (2.4 deaths per 1,000 patients) will die because of the surgical procedure.

Corpus callosotomy

Twelve studies meeting our inclusion criteria reported some form of seizure frequency outcome measure. The lack of control patients in these studies reduces their internal validity, however, explanations for seizure reduction in these individuals other than an effect of surgery may be considered implausible.

Based on our threshold analyses, the percentage of patients who are likely to achieve a 90 percent reduction in overall seizure frequency 2 years after corpus callosotomy is 20 percent (CI of 12 percent to 31 percent). Our threshold analysis suggests that 15 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to achieve a 90 percent reduction in overall seizure frequency before callosotomy could be considered to produce no additional benefit in seizure control. A separate meta-analysis suggests that 16 percent of patients (CI: 9 percent to 24 percent) will achieve no reduction in overall seizure frequency or show an increase in seizure frequency.

Our meta-analyses comparing patient characteristics in patients with successful and nonsuccessful surgery found that age at surgery, age at seizure onset, or duration of epilepsy prior to surgery has little or no effect on the success of surgery.

Based on our threshold analyses, 26 percent of patients are likely to become free of their most disabling seizures 2 years after corpus callosotomy (CI: 17 percent to 36 percent). Our

threshold analysis suggests that 20 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to become free of their most disabling seizures before callosotomy could be considered to produce no additional benefit in seizure control.

A second threshold analysis for patients free of generalized tonic-clonic seizures found significant heterogeneity among the effect sizes. A meta-regression determined that the date the studies ended accounted for the variation among studies. Using the results of this meta-regression, we estimated that in a study with an average end date the percentage of patients who are likely to become free of generalized tonic-clonic seizures 2 years after corpus callosotomy is 40 percent (CI: 29 percent to 50 percent). Our threshold analysis suggests that 30 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to become free of generalized tonic-clonic seizures before callosotomy could be considered to produce no additional benefit in seizure control.

Our third threshold analysis suggests that the percentage of patients who are likely to become free of atonic seizures 2 years after corpus callosotomy is 62 percent (CI: 50 percent to 72 percent). Our threshold analysis suggests that 55 percent of similar patients in similarly designed studies, but who did not receive surgery, would have to become free of atonic seizures before callosotomy could be considered to produce no additional benefit in seizure control.

Only one study on employment after corpus callosotomy is available. Consequently, the generalizability of its findings is uncertain, and too few studies are available to make firm, relevant evidence-based conclusions.

Available data about the effects of corpus callosotomy on IQ are derived from only a single study of 10 patients. This is too few studies and too few patients from which to draw firm evidence-based conclusions.

Data reported in 20 studies of corpus callosotomy suggest that approximately 3.6 percent of patients may experience a serious permanent complication, usually some form of partial paralysis, disconnection syndrome, or language difficulty. Approximately 22 percent of patients will experience mild or transient complications, though reporting differences among studies may render this latter figure an underestimate. Data reported in 18 studies of corpus callosotomy suggest that approximately 0.93 percent of patients (9.3 deaths per 1,000 patients) may die because of this surgical procedure. However, this figure is uncertain because deaths were reported in relatively small studies, and not in relatively large ones.

Corpus callosotomy may provides some benefits and but the risk of complications is still high relative to the benefits. This benefit versus risk assessment must be judged against a patient's current condition when evaluating the need for surgery.

Frontal lobe surgery

Eighteen studies of frontal lobe surgery met our inclusion criteria. The strength of any of our conclusions based on the data from these studies is reduced by the lack of adequate control groups and potential biases inherent in case series designs common to the studies of frontal lobe surgery. However, explanations for seizure reduction in these individuals other than the effect of surgery may be considered implausible.

Studies of frontal lobe surgery reporting seizure-free undefined, seizure-free with no auras, and Engel class I, suggest that the percentage of frontal lobe surgery patients who become "seizure-free" is somewhere between 24 percent and 100 percent. The variations in outcome reporting prevented any meaningful meta-analyses.

Frontal lobe surgery is not without potentially damaging consequences especially when the lesion lies near an important motor area. Our analysis of eight studies reporting serious

permanent complications from surgery estimated that approximately 8.4 percent of patients will experience some type of complication, primarily some form of partial paralysis. However, this figure may be inaccurate because only two studies reported complications. Data reported in three studies of frontal lobe surgery reported only one death among 96 patients. These data are insufficient to estimate the true death rate for this type of surgery.

Hemispherectomy

Eleven studies of hemispherectomy met our inclusion criteria. The strength of any of our conclusions based on the data from these studies is reduced by the lack of control groups and potential biases inherent in case series designs common to the studies of hemispherectomy. However, explanations for seizure reduction in these individuals other than the effect of surgery may be considered implausible.

Three studies meeting the inclusion criteria reported some measure of seizure-free status. As a whole, the studies indicate that some proportion of hemispherectomy patients are seizure-free 2 years after surgery, perhaps between 40 percent and 70 percent. The same studies indicate that about 7 percent of patients may receive no benefit from this surgery.

Hemispherectomy is not without potentially damaging consequences, especially the development of hydrocephalus. Our analysis of 10 studies with a total of 251 patients reported only two serious permanent complications from surgery (0.8 percent), a severe disability due to bilateral brain swelling and a coma. However, given the small number of patients examined in these 10 studies, this may not be a reliable estimate. Among the same studies, the percentage of patients developing a mild or transient complication was 21 percent. Hydrocephalus, usually requiring the surgical placement of a shunt, was considered a transient complication and accounts for the high percentage of patients with mild or transient complications. Data reported in 11 studies of hemispherectomy suggest that approximately 2.6 percent of patients (26 deaths per 1,000 patients) may die because of the surgical procedure.

Multiple subpial transection

Our assessment of the efficacy of MST was based on a minimum 6 month followup rather than a 24 month followup. The strength of any of our conclusions based on the data from these studies is reduced by the lack of adequate control groups and potential biases inherent in retrospective case series designs common to the studies of MST. However, explanations for seizure reduction in these individuals other than the effect of surgery may be considered implausible.

Among the studies reporting seizure-free patients, too few studies were available for a threshold analysis. Studies of MST used a variety of “seizure-free” outcome measurements and reported widely different estimates of the number of patients likely to become seizure-free after MST (0 percent to 79 percent). Estimates of the percentage of patients able to achieve a 90 percent reduction in seizure frequency varied from 25 percent to 90 percent. Similarly, the estimates for patients who do not benefit from MST vary from 0 percent to 42 percent. The data are inconsistent across studies and do not allow for firm conclusions as to the exact proportion of patients who will become seizure-free or not benefit from MST. Differences in how each outcome measure was recorded may account for the differences between studies. Patient age, pathology, the length of followup period, and the centers in which this new procedure was performed are also possible explanations for the variation in results. In the absence of long-term followup data, patient improvement after MST cannot be assumed permanent or long lasting.

MST is not without potentially damaging consequences especially since important motor areas are often transected. Our analysis of nine studies reporting serious permanent complications from surgery estimated that approximately 5.9 percent of patients would experience these types of complications, particularly aphasia or dysphasia. Data from seven studies of MST suggest that mild or transient complications may occur in 19 percent of patients. Although no deaths were reported in any of the studies in our evidence base for MST, this is likely to change as the procedure is used in more patients.

Nondrug, Nonsurgical Treatments

We assessed evidence pertaining to the effectiveness of several nondrug, nonsurgical treatments for patients with treatment-resistant epilepsy. These included; VNS, the ketogenic diet, magnetic therapy, vitamin B_6 therapy, herbal medicines, acupuncture, electrical brain stimulation, chiropractic therapy, cranial realignment, and hyperbaric oxygen therapy. Only one nondrug, nonsurgical treatment, VNS, was addressed by a minimum of five appropriate studies and was thus fully assessed.

Although the evidence base on VNS consisted of fourteen acceptable articles (two double-blinded RCTs and 12 case series), evidence-based conclusions could only be drawn from semi-quantitative analyses of data originating from the two RCTs. This was because we found evidence to suggest that data from the case series overestimated the effectiveness of the technology.

Trends in the data extracted from these two RCTs suggest that VNS, when applied as an adjunct intervention, safely provides limited symptom relief to some patients with treatment-resistant epilepsy. These findings are only generalizable to patients with similar characteristics to those included in the two RCTs. That is, patients in the age range of between 12 and 60 years of age with partial seizures, who were not considered candidates for surgery. Evidence-based conclusions about the effectiveness of VNS in other populations of patients with treatment-resistant epilepsy cannot be drawn.

Nonmedical Treatments

Social, psychological and psychiatric services for treatment-resistant epilepsy are poorly reported in the published literature. No intervention was sufficiently well reported for firm evidence based conclusions to be reached.

Employment and School

Currently, there are insufficient published data available to address the employment or schooling status of patients with treatment-resistant epilepsy.

Mortality Rate

Overall mortality rates appear to be higher among patients with treatment-resistant epilepsy than in the general population. The evidence for this conclusion stems from standardized mortality ratios (SMRs), which reflect the number of observed deaths divided by the number of expected deaths. The latter number is the number of deaths expected given the age distribution of the study population and the age-specific death rates in the general population. Because SMRs from different studies are not directly comparable, the magnitude of the mortality difference cannot be determined with precision. The SMRs for overall mortality ranged from 1.9 to 10.4.

Evidence from two large studies suggests that patient age may affect the magnitude of the mortality rate difference, with the greatest difference appearing in the pediatric age group. Studies of newly diagnosed patients suggest that the mortality rate is higher in the overall population of patients with epilepsy compared to the general population. There is insufficient evidence to determine whether a mortality difference exists between patients with treatment-resistant epilepsy and the overall population of patients with epilepsy.

Sudden unexpected death in epilepsy (SUDEP) appears to be a major cause of death among patients with treatment-resistant epilepsy, representing 6 percent to 55 percent of the total deaths in studies that reported relevant data.

Although only crude mortality ratios (CMRs, which are similar to SMRs but are not age-adjusted) could be calculated for drowning rates, the ratios are high enough in each study (even when using the most conservative estimate of expected drowning rates) to conclude that drowning rates are higher among patients with treatment-resistant epilepsy compared to the general population. Higher quality evidence is needed to determine the true magnitude of the difference in drowning rates. There is insufficient evidence to determine whether drowning rates are higher among patients with treatment-resistant epilepsy compared to the overall population of patients with epilepsy.

Although CMRs suggest that the accident-related mortality rate could be higher in patients with treatment- resistant epilepsy compared to the general population, better evidence (including SMRs) is needed for confirmation of this trend. Similarly, there is insufficient evidence to determine whether a difference in mortality exists between patients with treatment-resistant epilepsy and newly diagnosed patients. There is also insufficient evidence to determine whether automobile accident-related mortality is elevated among patients with treatment-resistant epilepsy.

Although some studies reported mortality rates due to aspiration among patients with treatment-resistant epilepsy, we found no comparable information in general population databases or studies of newly-diagnosed patients with epilepsy. Therefore, no firm evidence-based conclusions can be drawn.

Pneumonia mortality rates varied considerably among the studies that reported them, and this could have been due to differences in the mean age of the study groups. The study with the largest CMR had the oldest patient population. One study of newly diagnosed patients reported an SMR indicating a significantly higher pneumonia mortality rate compared to the general population, and this study examined a relatively older patient population. However, because the CMRs varied and SMRs could not be calculated for patients with treatment-resistant epilepsy, no firm conclusions can be drawn.

The CMR calculated from one mortality study of patients with treatment-resistant epilepsy did not show a difference in cardiovascular mortality rates between this group and the general reference population. Another study of newly diagnosed patients also reported an SMR that showed no cardiovascular mortality difference between these patients and the general population. However, the evidence is insufficient to allow firm conclusions.

CMRs of cerebrovascular mortality rates did not show a statistically significant difference between patients with treatment-resistant epilepsy and the general population, but SMRs are needed for confirmation. One study of newly diagnosed patients reported an SMR indicating a significantly higher cerebrovascular mortality rate among these patients compared to the general population. Again, more studies with SMRs are needed for confirmation. There is insufficient

evidence to determine whether a cerebrovascular mortality difference exists between patients with treatment-resistant epilepsy and the overall population of patients with epilepsy.

Only one of the studies reporting cancer mortality among patients with treatment-resistant epilepsy calculated SMRs. This study (also the study with the oldest patient group) found a significantly higher cancer mortality rate among these patients compared to the general population. Without more SMRs from additional studies, however, no firm evidence-based conclusions can be drawn. One study of newly diagnosed patients reported an SMR suggesting an elevated cancer mortality rate among these patients compared to the general population; this study also had an older patient population. There is insufficient evidence to determine whether the cancer mortality rate differs between patients with treatment-resistant epilepsy and the overall population of patients with epilepsy.

Only CMRs could be calculated from the three studies reporting suicide rates among patients with treatment-resistant epilepsy. The trends toward higher suicide rates among these patients compared to the general population were not statistically significant, but the evidence is insufficient to draw firm conclusions. There is likewise insufficient evidence to determine whether suicide rates differ between patients with treatment-resistant epilepsy and the overall population of patients with epilepsy.

Frequency and Type of Seizure and Sudden Death

The link between sudden unexpected death in epilepsy (SUDEP) and overall seizure frequency is uncertain. Most case-control studies did not find a statistically significant relationship between overall seizure frequency and SUDEP. Studies that performed multiple regression analysis (to adjust for the effects of variables other than seizure frequency that might influence SUDEP rates) were considered more reliable than studies that did not statistically adjust for the potential effects of other variables. Of the two studies that performed multiple regression analyses, one study found no statistically significant relationship after adjusting for frequency of tonic-clonic seizures. These findings are supported by the results of five of six lower quality studies that found no statistically significant association between overall seizure frequency and SUDEP (one other study did find a statistically significant association). However, four of these six studies may have had too little statistical power to detect such a relationship, and two of the four inadequately-powered studies showed a strong trend suggesting a relationship. The one remaining study that conducted multiple regression analysis found a statistically significant association after adjusting for other variables, but it did not adjust for the possible effect of frequency of tonic-clonic seizures. More evidence is needed before a firm evidence-based conclusion can be reached concerning the link between SUDEP and seizure frequency.

Although there is evidence in some studies concerning a relationship between the larger category of generalized seizures and SUDEP, the evidence is conflicting and insufficient to allow conclusions to be drawn. On the other hand, evidence from three studies (including one multiple regression analysis) suggests that tonic-clonic seizures may have an association with SUDEP. Since these were the only studies that looked specifically at tonic-clonic seizures and all showed the same result, this can be considered reasonable evidence of a relationship. This raises the possibility that a relationship between overall seizure frequency and SUDEP exists because some patients with more frequent seizures may be more likely to experience a life-threatening tonic-clonic seizure.