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Evidence Report/Technology Assessment

Number 77

Management of Treatment-Resistant Epilepsy

Summary

Overview

In this report, we evaluate and synthesize the published literature on diagnosis of, and medical and nonmedical interventions for treatment-resistant epilepsy. This report was commissioned upon the request of the Centers for Disease Control and Prevention and the Social Security Administration.

Epilepsy is a common, serious neurologic condition. An International League Against Epilepsy (ILAE) Commission Report from 1997 estimated the prevalence of active epilepsy as 40 to 100 in 10,000 and the incidence of unprovoked seizures as 2 to 7 per 10,000. However, precise estimates of prevalence and incidence are complicated by differences in the way investigators define epileptic and nonepileptic seizures (NES), and by the fact that prevalence is typically estimated using retrospective methods.

In addition to the immediate, debilitating effects of seizures, epilepsy also interferes with daily activities, and persons with epilepsy may have to contend with the increased possibility of accidental injury and even death. Psychiatric disorders may also be more common in people with epilepsy.

Persons with epilepsy often have impaired physical, psychological, and social functioning, which may lead to economic loss and diminished quality of life. A survey of 1,023 people with epilepsy published in 2000 showed that compared to U.S. Census Bureau norms, respondents received less education, were less likely to be employed, and were more likely to be members of low-income households.

Reporting the Evidence

This evidence report addresses nine key research questions encompassing 49 technologies, including several service-related interventions. However, the quantity and quality of published literature was insufficient to permit an evidence-based evaluation of 39 of these technologies. We therefore evaluated one diagnostic technology, three antiepileptic drug (AED) strategies, five surgical procedures, and one nondrug, nonsurgical intervention. In addition, we also surveyed the definitions of treatment-resistant epilepsy in the published clinical literature, with particular emphasis on the definitions reported in clinical studies.

The outcomes we considered depended upon the key research question. We used 16 patient-oriented outcomes to evaluate the effects of treatment, and all reported measures of diagnostic test performance. We also examined the rates of all-cause mortality and cause-specific mortality among persons with epilepsy.

Methodology

To obtain information for this report, we systematically searched 23 electronic databases, including PubMed® and EMBASE. In general, literature searches covered the years 1985 to January 1, 2002. For topics on AEDs, we searched for studies published between 1975 and January 1, 2002. We employed these earlier search dates to ensure that we captured data on standard drug treatments, which are likely to be in relatively older literature.

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We employed different search strategies for each of the nine key research questions. Searches were implemented by first developing a list of Medical Subject Headings (MeSH) terms, publication types, and textword combinations. This list included the concepts inherent in each of the key research questions. These searches identified 11,111 articles. From these identified articles, we retrieved 2,356 potentially relevant articles to determine whether they met the a priori criteria tailored for each key research question.

Three hundred forty-eight articles met these inclusion criteria. We next evaluated these articles to determine whether they contained design flaws so severe that their results were uninterpretable. Such articles were excluded. In addition, we excluded articles if there were fewer than five published studies on a given intervention or diagnostic, and none of the studies was a randomized controlled trial with 50 or more patients in the treatment arm. We adopted this latter criterion because of the difficulty in reaching firm evidence-based conclusions from a relatively small literature base comprised of studies of less than optimal design. As a result, 299 articles are included in this evidence report for key research questions 2-9. One hundred eighty-five articles for key research question 1 (on definitions of treatment-resistant epilepsy) were selected from all of the articles included in key research questions 2-6, from available clinical guidelines, and from a random sample of 100 review articles.

We employed a "best evidence" synthesis in this evidence report. Thus, for each key research question, we used the best available evidence, not the best possible evidence. Consequently, studies of several designs were included in this report. Diagnostic case-control studies are the most common design for diagnostic topics, randomized controlled trials (RCT) are most commonly used for evaluating AED strategies, and the surgical literature is comprised almost exclusively of retrospective case series.

We evaluated the internal validity of all included studies using checklists of biases that could potentially affect their results. In considering study design, we assumed that randomized controlled trials provide results with the least potential for bias. This was followed, in order of increasing potential for bias, by controlled studies of other design, studies that measured patient outcomes before and after some intervention, and uncontrolled studies. Among each type of study, we considered blinded studies to have lower potential for bias than nonblinded studies, and prospective studies to have lower potential for bias than retrospective studies.

In parts of this report, we used a systematic narrative review supplemented by numerous *de novo* calculations. These include calculations that index the statistical power of nonsignificant studies, various statistics (e.g., chi-square tests), crude mortality ratios, and other quantities, as appropriate. The majority of this evidence report is, however, meta-analytic.

We performed random effects meta-analyses on data from RCTs examining polytherapy AED treatment. We used sensitivity analyses to evaluate how robust the results of these analyses were. Sensitivity analyses consisted of removing the largest and smallest studies from the meta-analysis, and removing the studies with the largest and smallest effects. Each of the trials in these meta-analyses is an instance of polytherapy, rather than a direct study of this strategy. However, combining these trials into a single analysis of polytherapy can provide an approximate estimate of the effect of adding a single new AED to patients' regimens.

We performed threshold analyses on data from uncontrolled studies of sequential monotherapy and surgery. For sequential monotherapy, we employed random effects models, whereas for surgery we employed fixed effects models. We used random effects models for analyses of sequential monotherapy because of the heterogeneity among results of trials using different AEDs. In our threshold analyses, we meta-analytically compared the improvement rate in treated patients to increasing rates of improvement in a hypothetical "control" group. Starting at 0 percent, we increased the rate of improvement in the "control" patients until the difference in improvement between the treated and "control" groups was no longer statistically significant. This value is the threshold. Where possible, we provide context for these thresholds by supplementing them with historical data obtained from published articles.

We also report the percentage of patients who improved after the intervention (as given by the meta-analytic results when improvement in the control group is 0 percent), but note that this percentage is not a measure of the net effectiveness of the intervention. Some patients may have improved without treatment. Nevertheless, this percentage is informative because it represents the proportion of patients likely to improve, regardless of the cause of their improvement.

When heterogeneity among study results was found in a threshold analysis, we attempted to "explain" the source of the heterogeneity using meta-regression. Because of the lack of strong a priori hypotheses about the reasons for this heterogeneity, we constructed multiple meta-regression models for each instance in which heterogeneity was found. The post hoc nature of these analyses led us to adopt stringent criteria for identifying models for further exploration. These explorations consisted of threshold analyses of the regression intercepts.

Findings

Question 1: What are the definitions of treatment-resistant epilepsy used in the literature?

- Treatment resistance is infrequently defined in the literature. Less than one third of the surveyed publications reported any definition of this term.
- When treatment resistance was defined, definitions typically included the number of AEDs a patient tried before being considered treatment-resistant. Some definitions also included seizure frequency, duration of illness, and whether AEDs were administered at maximum tolerable doses.
- Drug trials tended to require fewer failures of AED treatment compared to surgical trials. This is because a very thorough assessment of drug regimens is usually attempted before surgery is considered. Assessments are usually less thorough when giving a patient another AED.
- Despite the fact that reports of clinical trials and review articles regularly use terms such as "intractable," "refractory," or "treatment-resistant" to describe patients for whom one or more treatments have failed, no consensus exists as to precisely what these terms mean.

Question 2: Which methods of rediagnosing or reevaluating treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?

We partitioned this question into four subquestions. The first two subquestions addressed differential diagnosis of epileptic seizures from nonepileptic seizures. The remaining two subquestions addressed the differential diagnosis of different seizure types. Whether we addressed some questions depended on the findings for previous questions.

Question 2A: Do all patients diagnosed with epilepsy that is deemed to be treatment-resistant truly have epilepsy?

This question attempts to gauge the extent of the need for rediagnosis among patients thought to have treatment-resistant epilepsy. Our evaluation of the published literature suggests the following:

- Meta-analysis suggests that up to 35 percent of patients originally diagnosed with treatment-resistant epilepsy either do not have epilepsy, or they have a combination of both epileptic and nonepileptic seizures. Because this number is derived from studies that enrolled patients suspected of having nonepileptic seizures, the actual number is probably lower.
- None of the studies included in the above-mentioned meta-analysis contained pediatric patients. Thus, the prevalence of pediatric patients diagnosed with treatment resistant epilepsy and who either do not have epilepsy or have a combination of both epileptic and nonepileptic seizures is unknown.
- These findings suggest that some patients enrolled in studies 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.

Question 2B: Which diagnostic modalities are useful in differentiating seizure types commonly mistaken for epilepsy from true epileptic seizures?

- A paucity of high-quality evidence limited our ability to draw evidence-based conclusions about measurement of serum prolactin levels as a diagnostic tool. Consequently, we were precluded from developing diagnostic decision-model algorithms that take into account the realities of clinical practice, where a differential diagnosis is based on information from many diagnostic technologies, not just information from a single diagnostic in isolation.
- The only relevant diagnostic supported by a sufficient quantity of literature to allow evidence-based analysis was serum prolactin. The relatively low quality of this literature, however, precludes firm evidence-based conclusions. Rather, this literature only allows the conclusion that serum prolactin levels could plausibly distinguish epileptic seizures from some nonepileptic seizures. Further research is required to determine whether the performance of this test is sufficient to warrant its use in clinical practice.
- Despite the importance of video-electroencephalography (vEEG) in diagnostic protocols aimed at differentiating epileptic seizures from nonepileptic seizures, we do not draw evidence-based conclusions regarding the diagnostic performance of this technology in the present report because less than five high quality studies were identified. The fact that evidence-based conclusions were not drawn should not be interpreted as evidence that this technology is not effective or useful. Indeed, vEEG may very well have an important role in diagnostic algorithms designed to differentiate patients with epilepsy from patients with nonepileptic seizure disorders. Until more high-quality studies become available, however, the diagnostic performance characteristics of vEEG and its place in such diagnostic algorithms cannot be determined.

Question 2C: Is seizure type in patients with treatment-resistant epilepsy misdiagnosed in some patients?

- There were too few acceptable studies addressing this question to permit analysis.

Question 2D: Which diagnostic modalities are useful in differentiating between different seizure types?

Because no evidence-based conclusions could be reached for Question 2C, the diagnostic modalities that are most useful in differentiating between different seizure types could not be determined.

Question 3: Is there evidence that patients with treatment-resistant epilepsy are not optimized at their current level of treatment?

- Not all patients with treatment-resistant epilepsy receive optimized AED treatment.
- The percentage of patients with treatment-resistant epilepsy who are not receiving optimized therapy is difficult to estimate. This is because of a lack of relevant, large, population-based studies. Further, many studies of AEDs do not report whether patients comply with their AED regimens.

Question 4: Which drug treatment strategy, (A) sequential monotherapy, (B) polytherapy, or (C) optimized current therapy leads to improved outcomes for patients with treatment-resistant epilepsy, and (D) what are the relative improvements obtained with each strategy?

Based on the recommendation of the partners, for the purposes of this question, sequential monotherapy is defined as changing a patient's drug regimen from one or many AEDs to a single, different AED. Polytherapy is defined as changing a patient's drug regimen from one or many AEDs to a different multiple-AED regimen. In this report, all polytherapy trials were trials of a single add-on AED. Optimized current therapy was defined as changing the dose and/or the frequency of administration. Based on the recommendation of the partners, we also included the removal of one or more drugs within this definition.

Question 4A: Sequential monotherapy

- During long-term studies, an estimated 89 percent of patients continued to have seizures when switched to monotherapy. The remaining 11 percent of patients were seizure-free during the studies. When short-term studies were included, 16 percent of patients were seizure-free. However, because these data come from studies that indirectly addressed this issue, whether sequential monotherapy is directly responsible for these patients becoming seizure-free cannot be determined.
- An estimated 16 percent of patients experienced a doubling of monthly seizure frequency during studies of sequential monotherapy.
- An estimated 14 percent of patients experienced a doubling of two-day seizure frequency during studies of sequential monotherapy.
- Sequential monotherapy required the removal of patients' prior AEDs, and in some patients the increases in seizure frequency were likely caused by this removal. Increases may be more likely in the subset of patients who switched from multiple AEDs to a single AED, but available data do not address this possibility.
- These findings suggest that sequential monotherapy is more likely to increases seizures than to eliminate seizures.
- One cannot determine the side effects (or their rates) associated with sequential monotherapy because 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 percent to 95 percent) experienced mild adverse reactions to the new monotherapy drug.
- An estimated 5 percent of patients exited studies of sequential monotherapy due to adverse effects.
- The findings listed above are applicable only to the drugs and doses examined in this report.
- There was insufficient evidence to draw firm conclusions about the influence of sequential monotherapy on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, ability to hold a driver's license, or mortality.

Question 4B: Polytherapy

- 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. However, recipients of these drugs are also more likely to experience adverse effects leading to trial exit than are placebo recipients (8 percent vs. 4 percent). Many patients (55 percent to 94 percent) experienced mild adverse effects while taking the new drugs.
- The preceding estimates of the effect of add-on therapy are based on random-effects meta-analyses that combined different AEDs. These estimates serve as approximate guides for future research on polytherapy. However, their generalizability may be limited to the drugs and doses in the included trials. Further, the apparent effectiveness of an add-on drug may depend on concurrent medications. Thus, the results may not be applicable to patients receiving other concurrent medications. Also, the results of these trials cannot be generalized to other implementations of the polytherapy strategy (e.g., the addition of two drugs).
- Insufficient evidence was available to draw firm conclusions about the influence of polytherapy on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, ability to hold a driver's license, or mortality.

Question 4C: Optimized Current Therapy

- Drug reduction may lead to increases in seizure frequency in at least some patients. Although some patients experience 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.

- Convincing evidence is lacking to suggest 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, at least with the AEDs considered in this report, may lead to increases in seizure frequency and provide little benefit.
- Due to limited data, no evidence-based conclusions could be drawn about optimized current therapy that employed dose increases or changes in frequency of administration.

Question 4D: Comparing AED Strategies

- No included studies directly compared the three AED strategies. Because of the different goals of optimized therapy and the other two AED strategies, these interventions cannot be compared. Differences in the severity of disease of patients given polytherapy and sequential monotherapy preclude quantitative comparison. However, sequential monotherapy was more likely to be harmful than to be beneficial. The reverse was true for polytherapy. These qualitative conclusions suggest that polytherapy may be clinically preferable to sequential monotherapy.

Question 5: Which methods of nondrug treatment for epilepsy after initial treatment failure lead to improved outcomes for patients with treatment-resistant epilepsy?

Question 5A: Surgical Interventions

Temporal Lobe Surgery

- Threshold analyses of retrospective data suggest that 2 years after temporal lobe surgery, 55 percent of patients are completely seizure-free, and 68 percent are free of complex partial seizures. The retrospective case series design of the studies reporting these outcomes prevents stating that these rates are the direct result of surgery, because some patients may have become seizure-free without surgery. However, 50 percent of similar patients who did not receive surgery in similarly designed studies would have to be seizure-free before concluding that surgery did not improve this outcome. Similarly, 65 percent of similar patients who did not receive surgery would have to be free of complex partial seizures before concluding that surgery had no effect on complex partial seizures. To put these thresholds in context, published data from one RCT suggest that only 8 percent of patients who do not receive surgery become seizure-free. This suggests that many patients are seizure-free because of temporal lobe surgery.
- Meta-analysis did not reveal any relationship between whether a patient becomes seizure-free after temporal lobe surgery and the patient's age at surgery, age at seizure onset, side of surgery, or the presence of simple partial seizures. Larger studies are required to prove that there is no relationship between these patient characteristics and the outcome of surgery.
- The rate of new cases of depression after surgery ranges from 4 percent to 24 percent. Why this range is so wide is not clear, and whether surgery was responsible for these new cases cannot be determined.
- Threshold analysis suggests that 3 percent of patients develop psychosis after surgery. However, data from one trial with similar patients who did not receive surgery suggest that as many as 2 percent of these patients develop psychosis. Two percent is also the threshold at which a relationship between surgery and the onset of psychosis becomes statistically nonsignificant. Therefore, surgery cannot be assumed responsible for new cases of psychosis.
- Threshold analysis suggests that after temporal lobe surgery, approximately 13 percent of patients experience clinically significant increases in IQ and 10 percent of patients experience clinically significant decreases in IQ. The threshold analysis suggests that surgery may not be responsible for these changes if 10 percent of similar patients who did not receive surgery experienced an increase in IQ, and 7 percent of similar patients who did not receive surgery experienced a decrease in IQ. Data from one trial suggest that without surgery, 5 percent of patients experience a decrease and 5 percent of patients experience an increase in IQ. Therefore, if there is an effect of surgery on IQ, it does not affect large numbers of patients.
- Approximately 2 percent of patients will experience permanent complications from temporal lobe surgery, primarily some form of partial paralysis. Data reported in studies of temporal lobe surgery reporting deaths due to surgery suggest that approximately 0.24 percent of patients will die because of the surgical procedure.
- There was insufficient evidence to draw firm conclusions about the influence of temporal lobe surgery on quality of life, memory, functional status or ability, ability to return to (or remain in) work, ability to return to (or remain in) school, or ability to hold a driver's license.

Corpus Callosotomy

- Threshold analyses suggest that 2 years after corpus callosotomy, 20 percent of patients have achieved a 90 percent or better reduction in overall seizure frequency. The retrospective case series design of the studies reporting this outcome prevents stating that these rates are the direct result of surgery, because some patients may achieve a 90 percent reduction in seizure frequency without surgery. However, 15 percent of similar patients who did not receive surgery would have to experience a 90 percent or better reduction before concluding that surgery did not improve this outcome. No studies were available to provide context for these figures. Given the severity of patients' conditions, however, surgery is the most likely cause of these seizure reductions.
- Despite the improvements seen in some patients, 16 percent of patients will achieve no reduction in overall

seizure frequency or show an increase in seizure frequency after corpus callosotomy.

- Threshold analysis suggests that 2 years after corpus callosotomy, 26 percent of patients will be free of their most disabling seizures. However, 20 percent of similar patients who did not receive surgery would have to become free of their most disabling seizures before concluding that surgery did not improve this outcome. No studies were available to provide context for these figures. Given the severity of patients' conditions, however, surgery is the most likely cause of these seizure reductions.
- Approximately 3.6 percent of patients will experience serious complications after corpus callosotomy, primarily some form of partial paralysis, disconnection syndrome, or language difficulty. The precise mortality rate associated with this procedure is uncertain.
- There was insufficient evidence to draw firm conclusions about the influence of corpus callosotomy on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, or ability to hold a driver's license.

Frontal Lobe Surgery

- Studies of frontal lobe surgery report that 2 years after surgery, 20 percent to 100 percent of patients will be "seizure-free" depending on how this outcome is defined. These variations in outcome reporting prevented any meaningful threshold analysis.
- Approximately 8.4 percent of patients will experience some type of complication after frontal lobe surgery, 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 from this type of surgery.
- There was insufficient evidence to draw firm conclusions about the influence of frontal lobe surgery on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, or ability to hold a driver's license.

Hemispherectomy

- Three studies reported that between 40 percent and 70 percent of patients who receive hemispherectomy are seizure-free 2 years after surgery. Approximately 7 percent of patients may receive no benefit from this surgery. The paucity of literature on this topic means that these rates are not precise. Given the severity of patients' conditions, however, surgery is the most likely cause of this improvement.
- Ten studies reported only two serious permanent complications from surgery (0.8 percent). 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. Data reported in 11 studies of hemispherectomy suggest that approximately 2.6 percent of patients (26 deaths per 1,000 patients) will die because of the surgical procedure.
- There was insufficient evidence to draw firm conclusions about the influence of hemispherectomy on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, or ability to return to (or remain in) school.

Multiple Subpial Transection

- Reported percentages of patients who are seizure-free six or more months after multiple subpial transection vary from 0 percent to 75 percent, depending on how "seizure-free" is defined. Similarly, the estimates for patients who do not benefit from this surgery vary from 0 percent to 42 percent. Consequently, the data are inconsistent across studies and do not allow for firm evidence-based conclusions as to the exact proportion of patients who will become seizure-free or who will not benefit from multiple subpial transection.
- Nine studies reporting serious permanent complications from surgery estimated that approximately 5.9 percent of patients experience these types of complications, particularly aphasia or dysphasia. Although no deaths were reported in any of these studies, they may be reported in future studies.
- There was insufficient evidence to draw firm conclusions about the influence of multiple subpial transection on quality of life, mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, or ability to hold a driver's license.

Other Surgery

- Too few studies were available to allow for an evidence-based evaluation of parietal or occipital lobe surgery.

Question 5B: Nondrug, Nonsurgical Interventions

- Trends from two RCTs suggest that vagal nerve stimulation (VNS), when applied as an adjunct intervention, safely provides limited seizure frequency reduction in some patients with treatment-resistant epilepsy. The precise degree of seizure reduction depends upon the specific measure of seizure frequency.
- Currently available evidence does not suggest a dramatic effect of VNS on quality of life.
- There was insufficient evidence to draw firm conclusions about the influence of VNS on mood, cognitive function, functional status/ability, ability to return to (or remain in) work, ability to return to (or remain in) school, or ability to hold a driver's license.
- Too few studies were available to allow for an evidence-based evaluation of ketogenic diets, chiropractic

procedures, acupuncture, hyperbaric oxygen therapy, herbal medicine and homeopathy, cranial realignment, magnetic therapy, electrical brain stimulation, and vitamin B6 therapy.

Question 6: Which social, psychological or psychiatric services for treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?

- There were too few acceptable studies addressing this question to permit analysis.

Question 7: What characteristics of treatment-resistant epilepsy interfere with ability to obtain and maintain employment, or attend and perform well in school?

- There were too few acceptable studies addressing this question to permit analysis.

Question 8: What is the mortality rate of patients with treatment-resistant epilepsy?

- Persons with treatment-resistant epilepsy are approximately 2 to 10 times more likely to die compared to people in the general population. This excess mortality in persons with treatment-resistant epilepsy is largest among younger individuals.
- Sudden unexpected death 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.
- Drowning rates are higher among treatment-resistant patients with epilepsy compared to the general population. Higher quality evidence is needed to determine the precise magnitude of the difference in drowning rates.
- There is insufficient evidence to determine whether accident-related mortality, or mortality due to pneumonia, aspiration, suicide or cancer is higher among persons with epilepsy compared to the general population.

Question 9: Is there a correlation between the number and/or type of seizure and sudden death?

- Generalized tonic-clonic seizures appear to increase the risk of sudden death.
- The relationship between overall seizure frequency and sudden death is uncertain.

Future 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. 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 patients are truly treatment-resistant by enrolling only subjects who are optimized and compliant with their current therapy.

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, 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. 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.

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 and, as a consequence, requires a prospective, randomized controlled trial.

Because a diagnosis of epilepsy is not made based on the findings of a single diagnostic technology, studies are needed to evaluate the effectiveness of different clinical algorithms that utilize data collected from combinations of diagnostic technologies. Again, this approach would require a prospective, randomized controlled trial.

Studies of treatment

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 and changes in these adverse effects on the new treatment regime. 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 is also needed and, if possible, individual patient characteristics should be reported 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.

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. 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 standardized mortality rates (SMRs) for overall mortality, but few studies have calculated separate SMRs for specific causes of death or subgroups of specific ages. 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).

Large prospective studies where all suspected sudden unexpected death in epilepsy (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. 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.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the ECRI Evidence-based Practice Center, under Contract No. 290-97-0020. It is expected to be available in May 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 77, *Management of Treatment-Resistant Epilepsy*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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