Definition of intractable epilepsy

Shobhit Sinha, MBBS, FRCP, **Khurram A. Siddiqui,** MBBS, FRCP.

ABSTRACT

لا تنحصر أهمية تعريف مرض الصرع المستعصي على تحديد عدم استجابة ما يزيد عن 40% من مرضى الصرع للأدوية الطبية فحسب، بل أيضاً لتسهيل التعرف على هؤلاء المرضى وعمل مقارنة فيما بينهم لأسباب بحثية. ولكن لا يزال يصعب علينا وضع تعريف نهائي لهذا المرض. تتأثر عدم استجابة مرضى الصرع للدواء بعدد من العوامل وهي كالتالي: عدد المرات التي لم يستجيب فيها المرضى للعلاج، ومعدل النوبات، ومدة عدم الاستجابة، ومتلازمة الصرع، وأسبابه. اتفقت معظم الأبحاث على عدد المرات التي لا يستجيب فيها الصرع للعقار والتي قد تصل إلى مرتين أو ثلاثة، ويعتبر كلاً من معدل النوبات وزمن حدوثها من العوامل المتغيرة. لقد اقترح المجلس العالمي لمكافحة الصرع تعريفا لمرض الصرع المستعصي وهو فشل المحاولات المبذولة في استخدام نوعين من الأدوية المضادة للصرع واللذين تم اختيارهما بعد الدراسة. ويمكن أن يكون هذا التعريف عملياً للاستخدام السريري والبحث العلمي، إلا أنه مع استحداث العلاجات الحديثة والمعلومات قد يحدث تغيير لهذا التعريف.

Defining intractable epilepsy is essential not only to identify up to 40% of patients refractory to pharmacological management, but also to facilitate selection and comparison of such patients for research purposes. The ideal definition still eludes us. Multiple factors including number of antiepileptic drug (AED) failures, seizure frequency and duration of unresponsiveness, etiology, and epilepsy syndromes are considered in formulating the definition of pharmaco-resistant epilepsy. Most definitions used in the literature agree on the number of AED failures, which seem to be 2 or 3, however, the seizure frequency and time factor are varied. The International League Against Epilepsy proposed a definition of drug-resistant epilepsy as a failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules. This for now, could provide an operational definition for clinical and research settings. However, with emergence of new data and novel treatments the criteria for intractability may change.

Neurosciences 2011; Vol. 16 (1): 3-9

From the Department of Neurology, Neurosciences Center, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Shobhit Sinha, Consultant Neurology & Epilepsy, Neuroscience Center, King Fahad Medical City, PO Box 59046, Riyadh 11525, Kingdom of Saudi Arabia. Tel. +966 (1) 2889999 Ext. 8321. Fax. +966 (1) 2889999 Ext. 1391. E-mail: ssinha@kfmc.med.sa

Epilepsy, in a patient-relevant fashion, may be defined as a complex, chronic clinical symptom arising from a variety of brain pathologies that produce excessive, synchronous, intermittent, abnormal, firing patterns of neurons in the cerebral cortex; in turn these paroxysmal neuronal discharges cause both recurrent seizures and other concomitant symptoms of brain pathology including disorders of neuronal health (memory, cognitive dysfunction), psychological health (depression, anxiety), and / or social health (loss of self esteem), to ultimately produce a complicated clinical state with enormous variability among the afflicted individuals.[1] More commonly, epilepsy is defined as a tendency to recurrent, spontaneous, and unprovoked seizures. This is one of the most common neurological disorders affecting at least 50 million people worldwide and carrying a point prevalence of 1%, and every year around 50-70 patients per 100,000 of population is added, mostly affecting children and the elderly.[2,3] Most patients can be managed with anti-epileptic drugs (AEDs), however 10-40% of patients would still continue to have seizures despite optimal treatment.[4-8] Defining intractable epilepsy is essential not only to identify such patients refractory to pharmacological management, but also to facilitate selection and comparison of such patients for research purposes. Our objective in this review is to look for an appropriate definition of intractability by reviewing the current literature and also to gain an insight into the mechanisms that lead to intractability and to reach a consensus.

Why do we need a definition for intractable epilepsy? Uncontrolled seizure adversely affects the life of not just the patient but society as a whole in a profound way. The patients suffer in terms of schooling, and employment, and are stigmatized.[9,10] In addition, they frequently suffer from psychiatric complications, especially depression and anxiety.[11,12] Mortality is increased especially secondary to seizure related accidents,[13] higher suicide rates,[12] and sudden unexpected death in epilepsy.[14] Also, there is mounting evidence that uncontrolled seizures can lead to deterioration in cognition and developmental function.[15] Although these patients who are not completely controlled on AEDs are in the minority, a considerable proportion of resources is

utilized for their care.[16,17] Some of these patients may be eligible for treatment besides medications such as surgery or vagal nerve stimulator implant.[18] This is especially true for young children who by the virtue of increased brain plasticity may have more complete and faster recovery of functions post intervention.[19] Therefore, there is a need for early and prompt identification of medically refractory patients. Foremost in this regard is to first define 'intractable epilepsy'. The definition of intractable epilepsy is imperative to study and compare various epidemiological, clinical, and management variables in a uniform pattern across the globe. Also, to understand the neurobiology of refractory epilepsy that can lead to development of novel treatment strategies, and improve overall patient care.

What would be the characteristics of ideal definition? The Oxford dictionary states the meaning of "intractable" as hard to control. So, in simple words, intractable epilepsy could be stated as hard to treat the symptom of seizures. However, the definition is a carefully constructed formal statement that captures the meaning, the use, the function, and the essence of a term or a concept, and especially for human illness is an extremely powerful statement that not only describes the condition objectively, but also addresses the potential prognosis. Regarding the ideal definition for intractable epilepsy, it should not only have a high sensitivity and specificity for prediction of seizure recurrence despite optimal medical management, but also should state the physician as well as patient's perspective. From a physician's point of view the intractability usually refers to pharmaco-resistance that would depend upon the accuracy of diagnosis, the epilepsy syndrome, and appropriate AED treatment failures. From the patient's perspective the medication side effects, coexisting impairments, and over all effect of the seizures on the quality of life should be encompassed. To date there is no single definition that satisfies all the above.

What are the components of intractability? Multiple factors should be considered in formulating the definition of refractory epilepsy. These can be divided into 2 subgroups: 1) those related to pharmaco-resistance and, 2) patient-related factors. The patient-related factors may include intolerance to AEDs, physical, mental, and social impairments affecting the quality of life. Since most of these are subjective and vary from person to person, it is not possible or practical to include these in a universal definition of intractable epilepsy. Instead, pharmaco-resistance has been extensively studied and referred to as "intractable" in almost all studies addressing this issue in the literature. Some of the determinants of drug resistance are number of AED failures, duration of unresponsiveness to medication and seizure frequency, etiology of epilepsy, and epilepsy syndromes. Based

on the current literature, there is a reasonably clear consensus regarding a few factors, while the data are variable regarding others.

What is the optimal number of drug failures before the patient would be considered pharmaco-resistant? As per Kwan and Brodie,[20] the chances of achieving seizure control with the third drug once the patient has failed 2 AEDs for correct seizure type in an adequate dose is not more than 5-10%. So, such patients, although they still have up to a 10% chance of seizure control, can be practically considered as a drug failure and may be considered for other treatment options. Some of these patients with TLE have 60% or higher probability of seizure control following surgery.[21] In some specific syndrome such as TLE, failure to only a single drug trial accurately predicts pharmaco-resistance at 2 years after onset.[7] Drug tolerance can lead to drug failure, and is commonly seen due to either pharmacokinetic reasons such as induction of AED metabolizing enzymes, or pharmacodynamic determinants leading to adaptation of AED targets, for example, by loss of receptor sensitivity, and so forth. These can explain complete loss of any AED activity following prolonged use as well as cross tolerance to other drugs.[22] Recently, novel mechanisms for drug resistance that may affect a broad range of AEDs are being identified. These include alterations in the drug transporter mechanisms by over expression of multidrug resistance (MDR) proteins such as P-glycoprotein (due to polymorphism of drug transporter genes, MDR1 or ABCB1) in the endothelial cells, thus, decreasing the permeability across the blood-brain barrier.[23,24] In addition, single nucleotide polymorphisms in the voltage gated sodium channel genes SCN1A, SCN2A, and SCN3A can also result in multi AED resistance.[25] Alterations in the expression of gap junction proteins such as Connexin 43 and Connexin 32 and may also cause reduced pharmaco-sensitivity.[26] With further advancement in technology and our understanding, prompt identification of these changes may assist in early recognition of pharmaco-resistance.

There are no clear data regarding the minimal seizure frequency before regarding epilepsy as intractable. Some studies suggest one seizure per month,[4] while other experts consider any seizure in the past 6 months to one year.[27,28] While this may provide insight into the clinical decision making of the physician, the effect of seizure frequency varies for each patient in terms of his or her age, lifestyle, personal expectations and objectives, and quality of life. For example, one seizure a year even though may be regarded as acceptable seizure control from a medical point of view, however, could still legally prevent a patient from driving and adversely effect the quality of life. Whereas, a few seizures in a year may

still be regarded as a good control in a young child with Lennox Gastaut Syndrome.

The duration of AED trial before labeling a patient as pharmaco-resistant is an important question without definite answer. The duration of AED trial would depend upon the baseline frequency of seizures and number of drug trials. A newly diagnosed epilepsy patient is generally started on a single medication that is slowly titrated up to achieve complete seizure control or until AED side effects start to manifest. A second medication is substituted or added if the first medication fails to control seizures, or is intolerable at the therapeutic dose. If a patient is having multiple seizures in a month, then a trial of 2 or more AEDs could be completed with a few months. However, with a few seizures in a year, the duration of the AED trial can extend for 2 or more years before regarding the disease as intractable. A trial of at least 2 AEDs appears sufficient before regarding epilepsy as intractable. Having said that, as per a study in children by Berg et al,[29] repeated remissions and relapses were common in patients who had failed trials of 2 different AEDs. In fact, after a median period of 10 years of follow-up from the second AED failure, 37% of patients were seizure free for at least a year, and 23% were seizure free for at least 3 years. In another study involving 155 adult patients with active epilepsy of at least 5 years duration, new drug changes lead to at least one year of remission in 28% of the patients.[30] In another cohort of 246 adult patients with refractory epilepsy who were followed for 3 years, Callaghan et al[31] reported 6 month remission in 15% of patients. Negative predictors for remission included a history of status epilepticus, younger age at intractability, number of failed drug therapies, and presence of mental retardation.[31]

The etiologies of epilepsy are multiple and age dependent. Studies looking at etiologies in adult-onset intractable epilepsy are inadequate. In a prospective study in children,[4] 50% of patients who were diagnosed to have intractable epilepsy at 18 months or more of follow up had non-idiopathic localization related syndromes. In another study of childhood TLE, Spooner et al[32] found an abnormal MRI to be the strongest discriminator between the pharmaco-resistant and controlled patient. With the availability of advanced neuroimaging especially MRI, more highly epileptogenic brain lesions are being recognized that are regarded as having increased chances of being intractable to AED management. These include malformations of cortical development,[33] metabolic disorders especially those affecting the grey matter (such as mitochondrial, peroxisomal disorders, and so forth), mesial temporal sclerosis, vascular malformation (such as A-V malformation, cavernous hemangioma, and so forth),

infections, traumatic lesions, and neoplasms (such as gangliogliomas, dysembryoplastic neuroepithelial tumor, and oligodendrogliomas).[34,35] Similarly, certain epilepsy syndromes are associated with a high risk of medical intractability. Some of these are Lennox Gastaut Syndrome, progressive myoclonic epilepsies, Ohtahara syndrome, Dravet syndrome, West Syndrome, Sturge-Weber syndrome, and Landau-Kleffner syndrome.[36,37]

Another factor that may contribute to intractability of a seizure is the patient's age at the onset of seizures, and initial seizure frequency. In 2 studies of intractable epilepsy in childhood, Berg and colleagues[4,38] found that age of seizure onset between 5-9 years of age was associated with a lowered risk of developing intractability. Also, patients younger than one year of age had the highest risk; however, as stated by the authors this could be explained by syndromic grouping in the multivariate analysis. Arts et al[27] did not find this in their Dutch cohort. The number of seizures, especially the high initial seizure frequency (within the first 6 months) was found to be a significant factor predicting pharmaco-resistance in multiple studies related to childhood epilepsy.[4,27,39,40] Other probable predictors for intractability include a history of status epilepticus,[31,38] focal EEG slowing,[27] and presence of mental retardation.[31,39]

Definitions in the literature. Varied definitions of intractable epilepsy have been used in the literature (**Table 1**). In the Dutch study,[27] the investigators prospectively looked at the variables available early in childhood epilepsy associated with a poor short-term outcome. With their definition of poor outcome as <6 months of remission at 2 years, they found that 30% of the patients in their cohort (466 children) had poor outcome, and seizure type, etiology, frequency, not attaining a 3-month remission and abnormal EEG at 6 months were predictive variables. The requirement for medication failure was not stated in their criteria. Casetta et al[40] carried out a community based case-controlled study in an Italian cohort to identify early predictors of intractability in childhood and adolescence epilepsy. They selected patients as intractable cases, who averaged at least one unprovoked seizure per month, and failed at least 3 medications. In their study, onset age less then one year, remote symptomatic etiology, and high frequency of seizures before therapy were found to be the early predictors of intractability. In the Nova Scotia pediatric epilepsy study, Camfield and Camfield[6] defined intractability as having one or more seizure every 3 months in the last year of follow up. Another study from Scotland,[20] stated their criteria as less than one year seizure free at the last follow up.

Dlugos and colleagues[7] retrospectively studied predictors for early identification of children destined to develop intractable TLE, which was defined as the

Table 1 - Definitions of intractable epilepsy used in the literature.

Author	Study objective	Study methodology	Definition used	Remarks
Arts et al (1999)[27]	To identify variables in early childhood epilepsy associated with poor outcome	Prospective chart review	Sz remission of <6 months at 2 years	Requirement of AED failure not included
Casetta et al (1999)[40]	To identify early predictors of intractability in childhood epilepsy	Prospective community based case-controlled	≥1 sz/month and ≥3 failed AEDs	The sz frequency was averaged during the observational period of 2 years
Camfield & Camfield (2005)[6]	To study frequency of intractable sz after stopping AED	Prospective population based chart review	≥1 sz/3 months and ≥3 failed AEDs	
Dlugos et al (2001)[7]	To determine predictors for early identification of intractability	Retrospective cohort	Persistence of sz between 18-24 months after epilepsy onset despite ≥2 AED trials	Study was carried out in pediatric patients with temporal lobe epilepsy
Spooner et al (2006)[32]	To determine factors predictive of long term sz outcome	Prospective community based cohort	Failure of ≥2 AEDs	Seizure frequency not used in the definition. Study was carried out in pediatric patients with temporal lobe epilepsy
Berg et al (2003)[41]	To look at the recruitment and selection of patients for epilepsy surgery	Prospective multicenter observational cohort	≥20 sz during previous 2 years and ≥2 failed AEDs	Used as eligibility criteria for surgery
Berg et al (2006)[42]	To determine when in course of epilepsy intractability becomes evident	Prospective observational cohort	Two definitions used: 1) 1 sz/month for 18 months and ≥2 failed AEDs 2) ≥2 failed AEDs only	With more stringent definition, only 14% of patients were deemed intractable versus 23% with the definition 2 in their cohort
Picot et al (2008)[43]	To study the prevalence of pharmacoresistant epilepsy	Prospective observational cohort	Two definitions used: 1) 1 sz/month for 18 month and ≥2 failed AEDs 2) 1 sz/year and ≥2 failed AEDs	The only epidemiological study carried out in a geographically defined adult population
Kwan et al (2010)[47]	ILAE Consensus proposal on definition of drug resistant epilepsy		Failure of an adequate trial of 2 tolerated and appropriately chosen AEDs	Authors provide scheme for categorizing outcome of drug trial

AED - antiepileptic drug, sz - seizure, ILAE - International League Against Epilepsy

persistence of any seizures involving impairment of consciousness between 18 and 24 months after epilepsy onset and despite at least 2 maximally tolerated AED trials. Three predictors of refractory TLE were found on bivariate analysis: an early risk factor for epilepsy, temporal lobe abnormality on MRI scan, and failure of the first AED trial. However, logistic regression indicated that the best model to predict refractory TLE contained only the variable "failure of first AED trial."[7] So, they concluded that the failure of the first AED trial accurately predicts refractory TLE at 2 years after onset. An Australian study[32] also looked at children with TLE, but in a prospective fashion, and concluded that the lesions on MRI predicted poor outcome. Their criterion for time to intractability was failure of 2 or more medications without the use of minimal seizure frequency. In a multi-center study, looking at recruitment and selection of patients for epilepsy surgery,[41] the eligibility criteria were stated as failure of at least 2 first line AEDs, and patients should have a minimum of 20 partial or secondary generalized seizures during the previous 2 years.

In 1996, Berg and colleagues,[38] in a retrospective case study looked at the predictors of intractable epilepsy in childhood. Their cases were children who had an average of one seizure or more a month over a 2-year period and who, during that time, had failed trials of at least 3 different AEDs. In their study, the independent

predictors of intractability were infantile spasm, age at onset with a decreasing risk with increasing age, remote symptomatic epilepsy, and status epilepticus. Berg et al[4] in 2001 prospectively studied the early development of intractable epilepsy in children. The definition used was minimal failure of 2 AEDs, more than one seizure a month and less than 3 consecutive months of seizure freedom. In their cohort of 613 patients, 10% met the criteria of intractable epilepsy with the risk factors being symptomatic generalized syndromes and high initial frequency of seizures. In 2006, the same author published the data collected prospectively to determine when in the course of epilepsy intractability becomes apparent.[42] They defined intractability in 2 ways. The stringent definition required failure of 2 drugs and seizure frequency of one/month on an average of 18 months; and the other definition stated failure of 2 AEDs. Fourteen percent (83 out of 613) of patients met the stringent and 23.2% met the other criteria. Intractability in their cohort strongly depended upon the syndrome, and may be delayed for 3 or more years especially in focal epilepsy.

The only study looking at the prevalence of pharmaco-resistant epilepsy was carried out by Picot and colleagues[43] in a geographically defined adult population in France using 2 definitions. The first definition required occurrence of seizures at an average frequency of at least one per month for 18 months, and the second required at least one seizure per year. Both definitions required failure of 2 medications. Using definition one, the prevalence rate was 0.9 per 1,000 (15.3% of patients with epilepsy), and with definition 2, the rate was found to be 1.4 per thousand (22.1%). The study provides an invaluable insight into the burden of intractable epilepsy in the population and may assist the administrators in efficiently allocating the resources in care of these patients.

One study from Qatar retrospectively reviewed 219 patients with epilepsy seen over a period of 8 years to determine the incidence and causes of intractable epilepsy amongst adults.[44] Intractable epilepsy was defined as occurrence of 2 or more seizure episodes per month despite adequate mono- or poly-therapy of AED medication for at least 2 years. Thirty-nine patients (18%) were determined to have refractory seizures and the incidence was approximated at 4.5 per 100,000 persons.

Comparing the above definitions, the common elements defining intractability are: number of AEDs that need to be failed, the seizure frequency, and time period during which the seizure is observed. The consensus regarding the number of AED failure seems to be 2 or 3. However, the seizure frequency and time factor are variable across the studies. Also, some studies did not use all 3 elements to define their poor outcome. Berg and Kelly[45] did a head to head comparison between some of the definitions and concluded that these definitions had high (83-96%) absolute agreement, although agreement corrected to chance (kappa) ranged from 0.39 (poor) to 0.79 (excellent). Most of the studies were carried out on children with epilepsy, so data are limited for intractable epilepsy with onset during adulthood or in the elderly.

Consensus. The perfect definition of intractable epilepsy suiting all purposes still remains elusive and is like defining the indefinable.[46] In order to promptly recognize pharmaco-resistance as it occurs, it may be more important to have different criteria for different types/presentations of epilepsy. The definition may be specific for a child with malignant seizures (as those seen with West syndrome or Lennox Gastaut syndrome) versus an adult with localization related epilepsy. Also, the definition may vary as per the clinical setting. This means that there should be a set of fixed criteria to guide a general practitioner to refer the patient to a specialist, or to advise the specialist to pursue non-pharmacological interventions.

The Task Force of the International League Against Epilepsy (ILAE) commission on Therapeutic Strategies published a consensus proposal on the definition of drug resistant epilepsy.[47] The ILAE definition comprises 2 hierarchical levels: level one provides a general scheme to categorize the outcome of each therapeutic intervention (for example, an AED) as "seizure freedom" (seizure freedom defined as freedom from seizures for a minimum of 3 times the longest pre-intervention inter-seizure interval or 12 months, whichever is longer) or "treatment failure" (treatment failure is defined as recurrent seizure(s) after the intervention is adequately applied).[47] The drug trials that are "uninformative" for determining efficacy must be regarded as "undetermined" (undetermined is defined as when the treatment has not been adequately applied for a valid assessment of the outcome, or information is lacking to make the assessment).[47] This occurs when an AED has been inadequately tried due to, for example, early withdrawal owing to an allergic skin rash, poor tolerability, psychosocial reasons (such as planning for pregnancy), affordability, and so forth. Level one forms the basis for level 2, which defines drug-resistant epilepsy as "a failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[47]

The ILAE definition, for now, could be the operational definition that would guide health care professionals, especially general practitioners, in referring such patients to tertiary epilepsy care centers for further assessment and management. Besides this, it can also be utilized for

clinical and basic research purposes. This would provide uniformity in patient selection and facilitate analysis of results of various outcome studies across the board without the worry of different inclusion criteria, which was the major limitation in past. It would also help in prompt recognition of treatment resistant patients that would aid in determination of epidemiology of drug resistant epilepsy for better allocation of healthcare and other resources. With time and emergence of new data, the validity of the definition would be tested and if required may be further modified. In addition, with the availability of new improved medical treatments the remission rate for epilepsy may improve and the criteria for intractability may change.

References

1. Weaver DF. Patient-relevant, rather than physician-friendly, definitions of disease: an improved definition of epilepsy. *Am J Med* 2005; 118: 805-806.
2. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998; 352: 1970-1973.
3. Kotsopoulos IA, van Merode T, Kessels FG, de Krom MC, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia* 2002; 43: 1402-1409.
4. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001; 56: 1445-1452.
5. Sillanpaa M. Remission of seizures and predictors of intractability in long-term follow-up. *Epilepsia* 1993; 34: 930-936.
6. Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. *Neurology* 2005; 64: 973-975.
7. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. *Neurology* 2001; 57: 2259-2264.
8. Kwan P, Brodie MJ. Drug treatment of epilepsy: when does it fail and how to optimize its use? *CNS Spectr* 2004; 9: 110-119.
9. Obeid T. Stigma. An aspect of epilepsy not to be ignored. *Saudi Med J* 2008; 29: 489-497.
10. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. *Epilepsy Behav* 2008; 12: 540-546.
11. Brandt C, Schoendienst M, Trentowska M, May TW, Pohlmann-Eden B, Tuschen-Caffier B, et al. Prevalence of anxiety disorders in patients with refractory focal epilepsy--a prospective clinic based survey. *Epilepsy Behav* 2010; 17: 259-263.
12. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 2003; 54: 388-398.
13. Sheth SG, Krauss G, Krumholz A, Li G. Mortality in epilepsy: driving fatalities vs other causes of death in patients with epilepsy. *Neurology* 2004; 63: 1002-1007.
14. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001; 56: 519-525.
15. Thompson PJ, Duncan JS. Cognitive decline in severe intractable epilepsy. *Epilepsia* 2005; 46: 1780-1787.
16. Pugliatti M, Beghi E, Forsgren L, Ekman M, Sobocki P. Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia* 2007; 48: 2224-2233.
17. Strzelczyk A, Reese JP, Dodel R, Hamer HM. Cost of epilepsy: a systematic review. *Pharmacoeconomics* 2008; 26: 463-476.
18. Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003; 60: 538-547.
19. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia* 2005; 46: 561-567.
20. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-319.
21. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345: 311-318.
22. Loscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia* 2006; 47: 1253-1284.
23. Marchi N, Gonzalez-Martinez J, Nguyen MT, Granata T, Janigro D. Transporters in drug-refractory epilepsy: clinical significance. *Clin Pharmacol Ther* 2010; 87: 13-15.
24. Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, Goldstein DB, et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 2003; 348: 1442-1448.
25. Kwan P, Poon WS, Ng HK, Kang DE, Wong V, Ng PW, et al. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. *Pharmacogenet Genomics* 2008; 18: 989-998.
26. Aronica E, Gorter JA, Jansen GH, Leenstra S, Yankaya B, Troost D. Expression of connexin 43 and connexin 32 gap-junction proteins in epilepsy-associated brain tumors and in the perilesional epileptic cortex. *Acta Neuropathol* 2001; 101: 449-459.
27. Arts WF, Geerts AT, Brouwer OF, Boudewyn Peters AC, Stroink H, van Donselaar CA. The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. *Epilepsia* 1999; 40: 726-734.
28. Kwan P, Brodie MJ, Epilepsy after the first drug fails: substitution or add-on? *Seizure* 2000; 9: 464-468.
29. Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: a prospective study. *Ann Neurol* 2009; 65: 510-519.
30. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007; 62: 375-381.
31. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol* 2007; 62: 382-389.
32. Spooner CG, Berkovic SF, Mitchell LA, Wrennall JA, Harvey AS. New-onset temporal lobe epilepsy in children: lesion on MRI predicts poor seizure outcome. *Neurology* 2006; 67: 2147-2153.
33. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development: update 2001. *Neurology* 2001; 57: 2168-2178.

34. Whiting S, Farrell K, Wirrell E. Diseases and syndromes associated with intractable epilepsy. *Adv Neurol* 2006; 97: 443-462.

35. Nolan MA, Sakuta R, Chuang N, Otsubo H, Rutka JT, Snead OC 3rd, et al. Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. *Neurology* 2004; 62: 2270-2276.

36. Nordli DR Jr. Infantile seizures and epilepsy syndromes. *Epilepsia* 2002; 43 Suppl 3: 11-16. Review.

37. Wheless JW, Kim HL. Adolescent seizures and epilepsy syndromes. *Epilepsia* 2002; 43 Suppl 3: 33-52. Review.

38. Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case-control study. *Epilepsia* 1996; 37: 24-30.

39. Brorson LO, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987; 28: 324-330.

40. Casetta I, Granieri E, Monetti VC, Gilli G, Tola MR, Paolino E, et al. Early predictors of intractability in childhood epilepsy: a community-based case-control study in Copparo, Italy. *Acta Neurol Scand* 1999; 99: 329-333.

41. Berg AT, Vickrey BG, Langfitt JT, Sperling MR, Walczak TS, Shinnar S, et al. The multicenter study of epilepsy surgery: recruitment and selection for surgery. *Epilepsia* 2003; 44: 1425-1433.

42. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, et al. How long does it take for epilepsy to become intractable? A prospective investigation. *Ann Neurol* 2006; 60: 73-99.

43. Picot MC, Baldy-Moulinier M, Daurès JP, Dujols P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia* 2008; 49: 1230-1238.

44. Al Hail H, Sokrab T, Hamad A, Kamran S, Hamad A, A/R, Khalid A. Epidemiology and Etiology of Intractable Epilepsy in Qatar. *Qatar Medical Journal* 2004; 13 (1).

45. Berg AT, Kelly MM. Defining intractability: comparisons among published definitions. *Epilepsia* 2006; 47: 431-436.

46. Kwan P, Brodie MJ. Definition of refractory epilepsy: defining the indefinable? *Lancet Neurol* 2010; 9: 27-29.

47. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; 51: 1069-1077.

Related topics

Hussein K, Khan S. Efficacy and safety of vagus nerve stimulation for intractable epilepsy at Riyadh Military Hospital: A one-year follow up study. *Neurosciences (Riyadh)* 2008; 13 (Suppl): 45.

Mohamed GF. Strategy of management of intractable epilepsy. *Neurosciences (Riyadh)* 2008; 13: 44.

Girvin JP, Baeesa SS. Functional hemispherectomy for the treatment of intractable seizures. *Neurosciences (Riyadh)* 2006; 11: 72-77.

Hamad A. Clinical experience with diazepam rectal gel in adult patients with mental retardation and intractable epilepsy. *Neurosciences (Riyadh)* 2004; 9: 82.