Original article

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Treatment of pediatric epilepsy: European expert opinion, 2007

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ABSTRACT – *Background.* Childhood epilepsies are a heterogeneous group of conditions that differ in diagnostic criteria and management and have dramatically different outcomes. Despite increasing data on treatment of epilepsy, research findings on childhood epilepsy are more limited and many clinical questions remain unanswered, so that clinicians must often rely on clinical judgment. In such clinical situations, expert opinion can be especially helpful. *Methods.* A survey on pediatric epilepsy and seizures (33 questions and approximately 650 treatment options) was sent to 57 European physicians specializing in pediatric epilepsy, 42 (74%) of whom completed it. In some questions, the experts were asked to recommend overall treatment approaches for specific syndromes (the order in which they would use certain strategies). Most of the questions asked the experts to rate options using a modified version of the RAND 9-point scale for medical appropriateness. Consensus was defined as a non-random distribution of scores by chi-square test, with ratings used to assign a categorical rank (first line/usually appropriate, second line/equivocal, and third line/usually not appropriate) to each option. *Results.* Valproate was treatment of choice for symptomatic myoclonic and generalized tonic-clonic seizures. For initial monotherapy for complex partial seizures, carbamazepine and oxcarbazepine were treatments of choice, with valproate also first line. As initial therapy for infantile spasms caused by tuberous sclerosis, viagabatrin was treatment of choice. As initial therapy for infantile spasms that are symptomatic in etiology, vigabatrin was also treatment of choice, with adrenocorticotropic hormone (ACTH) and prednisone other first-line options. As initial therapy for Lennox-Gastaut syndrome, valproate was treatment of choice. For acute treatment of a prolonged febrile seizure or cluster of seizures, rectal diazepam was treatment of choice. Valproate was treatment of choice as preventive therapy for febrile seizures. For benign childhood epilepsy with centro-temporal spikes, valproate was treatment of choice. For childhood and juvenile absence epilepsy, valproate was treatment of choice, with lamotrigine another first-line option (ethosuximide was another first-line option for childhood absence epilepsy). For juvenile myoclonic epilepsy in adolescent males, valproate was treatment of choice, with lamotrigine another first-line option; for juvenile myoclonic epilepsy in adolescent females, lamotrigine was treatment of choice, with valproate another first-line option. As initial therapy for neonatal status epilepticus, intravenous (IV)

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phenobarbital was treatment of choice. As initial therapy for all types of pediatric status epilepticus, IV diazepam was treatment of choice. For generalized tonic-clonic status epilepticus, rectal diazepam and IV lorazepam were also treatments of choice; for complex partial status epilepticus, IV lorazepam was another first-line option. *Conclusion*. The expert panel reached consensus on many treatment options. Within the limits of expert opinion and with the understanding that new research data may take precedence, the experts' recommendations provide helpful guidance in situations where the medical literature is scant or lacking. The information in this report should be evaluated in conjunction with evidence-based findings.

Key words: pediatric epilepsy, expert opinion, consensus, antiepileptic drugs, seizures, epilepsy syndromes

Expert consensus panel

The following participants in the Expert Consensus Survey were selected based on recent publications and national recognition and represent a geographic cross section of Europe. Of the 57 experts to whom we sent the epilepsy survey, 42 (74%) replied. The recommendations in this publication reflect the aggregate opinions of the experts and do not necessarily reflect the opinion of each individual on each question.

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Introduction

Seizure disorders are among the most frequent neurologic problems that occur in childhood. Childhood epilepsies are a heterogeneous group of conditions that differ in their diagnostic criteria and management and have dramatically different outcomes. Children and their parents deserve to receive treatment based on the best possible recommendations appropriate to the particular type of epilepsy. Eight new antiseizure medications (Anhut *et al.* 1994, Cereghino *et al.* 2000, Goa *et al.* 1993, Gram 1997, Kramer and Reife 1997, Sachdeo *et al.* 1997, Theodore 1997, US Gabapentin Study Group 1993, White 1999) were approved by the U.S. Food and Drug Administration (FDA) between 1993 and 2005. New formulations of older drugs (Wheless and Venkataraman 1999) and the vagus nerve stimulator (Wilder 1997) have become mainstays in the treatment of recurrent seizures. This decade also saw renewed use of the ketogenic diet (Kossoff and McGrogan 2005, Vining 1997) Finally, a number of antiseizure medications that are available only in some countries (e.g., clobazam [Brodie 2001, Montenegro *et al.* 2001, Ng and Collins 2007, Shmizu *et al.* 2003, Silva *et al.* 2006], vigabatrin [Thiele 2004, Wheless *et al.* 2007], stiripentol [Bialer *et al.* 2007, Chiron 2007, Chiron *et al.* 2000], and sulthiame [Ben-Zeev *et al.* 2004, Debus and Kurlemann 2004, Kramer *et al.* 2002]) are being used in the treatment of new onset and difficult-to-treat epilepsy. Epilepsy surgery is widely used as a treatment for refractory partial seizures, with recent evidence suggesting that surgery performed earlier after the diagnosis of refractory epilepsy may provide greater benefit than surgery performed after many years of intractable seizures (Wiebe 2004, Wiebe *et al.* 2001, Yasuda *et al.* 2006). New epilepsy therapies continue to be developed, with a new medication, pregabalin (Arroyo *et al.* 2004, Beydoun *et al.* 2005, French *et al.* 2003) launched in the fall of 2005. Trials of new devices for the treatment of epilepsy are also underway.

The increasing number of new treatments promises a better quality of life for individuals with epilepsy *(table 1)*. However, the ever-growing list of options also makes it much more difficult to select the optimal treatment or combination of treatments. Because the medical literature may not provide information regarding the use of a therapy in a particular clinical situation, clinicians must at times rely on their medical judgment: it is in this "gray area" where expert opinion can be most helpful.

To make treatment decisions, physicians rely on many sources of information. The highest level of evidence (Class I), often considered the least biased, is based on randomized clinical trials. In these trials, a therapeutic dose of active therapy is compared with a sub-therapeutic dose or placebo in order to evaluate the efficacy of the treatment. These trials also assess adverse events (safety and tolerability). One limitation of randomized clinical trials is that they are usually performed in patients with highly treatment-resistant illness, and such patients may not be representative of general clinical populations. In addition, randomized clinical trials rarely compare two or more active therapies, and therefore do not answer broader questions about which therapy is superior (more effective or better tolerated).

Given the limited number of head-to-head comparison trials, several authors have proposed the use of meta-analysis. Meta-analyses compare medication efficacy and tolerability using data derived from initial randomized clinical trials (Privitera 1999, Williamson *et al.* 2000). Although powerful tools, meta-analyses have limitations. An optimum dose and titration schedule for therapy may not have been used in the preliminary studies. For example, if the medication was used at a lower than optimum dose, efficacy would be underestimated. Conversely, if the medication was increased rapidly or titrated to a higher than optimum dose, the rate of adverse effects would be overestimated. Finally, the patient populations and study designs used in randomized clinical trials are not uniform, making direct comparisons between studies less reliable (Privitera 1999).

In addition to randomized clinical trials and meta-analyses, clinicians use non-randomized or uncontrolled clinical trials, retrospective reviews, case series, and case reports to help make clinical decisions (Class IV evidence). Although these are valuable sources of information, the data are obtained in a less rigorous manner than in randomized clinical trials. The lack of control subjects, possible investigator bias, and the small number of patients further erode the power of the results.

Table 1. Approval dates of antiepileptic drugs commonly prescribed in Europe.

Drug name	Approval dates in some European countries	Date of European Union marketing authorization approval[a]
Gabapentin	1993–95[b]	
Lamotrigine	1990–95[b]	
Levetiracetam		September 2000
Oxcarbazepine	1987–2000[c]	
Pregabalin		July 2004
Stiripentol		January 2007
Sulthiame	Mid-1960s[d]	
Tiagabine	1996–97[b]	
Topiramate	1993[c]	
Vigabatrin	1989[e]	
Zonisamide		March 2005

[a]Source: website of the European Medicines Agency (EMEA), http://www.emea.europa.eu (accessed September 5, 2007), [b]Loiseau 1999, [c]Gil-Nagel 2003, [d]Green *et al.* 1974, [e]Browne *et al.* 1991.

Despite the ever-growing body of evidence in the medical literature regarding the treatment of epilepsy, many routine clinical questions remain unanswered or only partially answered. Many of the common epilepsies that occur in childhood have no adult counterpart; others begin in childhood and may persist into adulthood. *Table 2* shows data on the incidence of epilepsy in the United States from 1990. Epidemiologic studies of epilepsy have revealed similar prevalence rates overall in Europe and North America (Forsgren 2004).

Very few of the available clinical trials for these common childhood epilepsies have compared different treatments with each other or provide guidance concerning an overall treatment strategy. In addition, many controlled trials do not include childhood epilepsies or epilepsy syndromes (e.g., symptomatic myoclonic or generalized tonic-clonic seizures, juvenile absence epilepsy, neonatal seizures, juvenile myoclonic epilepsy). Thus, physicians must very often rely on their own medical judgment to select the "best" treatment option for an individual patient. In this situation, physicians look to their colleagues and to expert opinion to help "fill in the gaps" left by randomized clinical trials. It is in such clinical situations that a summary of expert opinion can be most helpful.

Two prior surveys of experts in the United States have been done to fill in similar gaps in our knowledge of the treatment of epilepsy in adults (Karceski *et al.* 2001, 2005). However, those surveys did not specifically address the treatment of childhood epilepsies, prompting the initiation of a survey concerning treatment of childhood epilepsy. The results of that survey, which was completed by a group of 39 well respected experts on pediatric epilepsy in the United States in 2004–2005, were published in a supplement to the *Journal of Child Neurology* in December 2005 (Wheless *et al.* 2005). The recommendations in that supplement represented the first use of the expert consensus survey method in the field of pediatric epilepsy.

Three surveys of practicing neurologists have also been performed outside the United States. Baldy-Moulinier *et al.* (1998) performed an international survey of Mediterranean countries, surveying the opinions of 500 physicians from 14 countries. This survey only addressed treatment preferences for febrile, partial, and primary generalized tonic-clonic seizures. A Brazilian survey performed in 2002 (Betting *et al.* 2003) addressed the same topics as in the original adult epilepsy survey in the United States by Karceski *et al.* (2001). Finally, a recent Canadian study (Burneo and McLachlan 2007) surveyed 41 physicians in that country regarding the treatment of five common epilepsy syndromes or seizure types.

Table 2. Estimated number of children (< 18 years of age) with newly diagnosed seizures (U.S., 1990).

	N/year
Febrile seizures	100 000
Neonatal seizures	4 000
Epilepsy	30 000
Absence seizures	4 000
Juvenile myoclonic epilepsy	1 500
Benign partial epilepsy	3 000
Infantile spasms	1 000
Lennox-Gastaut Syndrome	250

Source: modified from Hauser 1994.

Expert opinion

There are many ways to gather opinion, and each has its advantages and disadvantages. Many people are familiar with "a roundtable discussion" where expert opinions or recommendations are summarized as a report of a formal meeting. However, there are two main limitations to this type of information. The first is bias: in small groups, or those led by an executive committee, a strong personality can influence others in the group, thereby steering the recommendations. Second, the groups of experts tend to be small and may not reflect the approach of a larger group of physicians (Kahn *et al.* 1997).

One way to eliminate this bias is to minimize the interaction between participants. There are several possible ways to accomplish this. First, a group can be given a series of questions, and asked to write down their responses (without consulting their colleagues). Their written results are then tabulated and summarized. Second, a group of experts can be polled using a mail-in survey. Here again, the results can be tabulated. The Rand method, developed in 1948, uses such an approach (Brook *et al.* 1986, Dalkey 1969, Woolfe 1992). However, the Rand method does not statistically analyze the results, limiting its usefulness as a tool.

The expert consensus method is a recently developed technique that statistically analyzes the results of expert opinion. The expert consensus method is based on the Rand method, but uses a quantitative analysis of responses to a mail-in survey to determine where opinions converge: when the experts agree, they have reached consensus, the origin of the name of the method itself (Frances *et al.* 1998, Kahn *et al.* 1997). The expert consensus method offers several advantages over previous methods. The use of the mail-in survey minimizes bias since the response of each expert is given equal weight. The mail-in survey minimizes interactions between participants, eliminating some of the potential bias. Experts from different geographic areas are polled in order to gather a representative cross section of practices within a larger area (for example, this survey was sent to experts in a number of different countries in Europe to gather a representative cross section of practices in Europe). Finally, a mail-in survey allows a large group of

experts to be polled, again minimizing biases that might arise from the analysis of responses from a small group of people. Statistical methods are then applied to the answers (see description of methods below). The results can be used to develop treatment recommendations: where possible, these are presented in an easily readable format (Kahn *et al*. 1997).

To date, this method has been applied primarily to a variety of psychiatric disorders (Allen *et al*. 2001 and 2005, Alexopoulos *et al*. 1998, 2001, 2004, and 2005, Altshuler *et al*. 2001, Conners *et al*. 2001, Foa *et al*. 1999, Kahn *et al*. 1996, Kane *et al*. 2003, Keck *et al*. 2004, March *et al*. 1997, McEvoy *et al*. 1996 and 1999, Rush and Frances 2000, Sachs *et al*. 2000), although it has also been used in three surveys to develop recommendations for the treatment of epilepsy in adults, children, and adolescents (Karceski *et al*. 2001 and 2005, Wheless *et al*. 2005).

Methods

The experts

A group of 57 experts was identified, all of whom are physicians in Europe who specialize in pediatric epilepsy, 42 (74%) of whom completed the survey. Surveys were returned between January 2005 and April 2006. The experts, selected based on regional stature and recent publications, are considered leaders in the field of pediatric epilepsy and represent a geographic cross section of Europe. No honorarium was provided. No commercial support was received to conduct the survey and develop the recommendations. A grant from the Shainberg Foundation supported publication of the results.

The survey

Given that prevalence rates of epilepsy appear to be similar in Europe and North America (Forsgren 2004), it was considered appropriate to survey European experts concerning the same syndromes that were the focus of an earlier survey of American experts on pediatric epilepsy (Wheless *et al*. 2005). The survey described in this publication was adapted from that earlier U.S. survey for use in Europe by adding medications that are available in some European countries but not in the United States for the appropriate seizure types. Designed to address key decision points in the management of epilepsy and seizures in pediatric patients, the survey contained 33 questions in which the experts were asked to provide their opinion regarding approximately 650 treatment options. The survey asked about symptomatic myoclonic and generalized tonic-clonic seizures, complex partial seizures, neonatal seizures, infantile spasms, Lennox-Gastaut syndrome, febrile seizures, benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy), absence epilepsy, juvenile myoclonic epilepsy, newly diagnosed epilepsy in the emergency department, and status epilepticus. For each of the syndromic diagnoses, the questions first focused on overall treatment strategies and then asked about choice of specific treatments.

Two types of questions were used. The first type was designed to identify an overall approach to the treatment of a specific epilepsy syndrome. In these questions, the

1) Symptomatic Myoclonic and Generalized Tonic-Clonic Seizures: Overall Strategy

A healthy 2-year-old child with developmental delay is diagnosed with myoclonic and generalized tonic-clonic seizures and has not been treated yet. Assume the family is amenable to all possible therapies and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

Using the letter that is listed at the left of each choice, please indicate the strategy you would use in the treatment of this patient. In the space marked "Step 1," indicate your first approach to treatment. If the first treatment fails to adequately control the seizures or is poorly tolerated, indicate your second choice (Step 2). For each step, you may list more than one treatment if there are treatment approaches you consider equivalent. You may use a letter only once. Do not leave blank spaces.

A. Monotherapy
B. Monotherapy 2nd agent (assume that there will be a period of time when the patient will receive two drugs during transition)
C. Monotherapy (additional trials)
D. Combination of 2 AEDs
E. Combination of 2 AEDs (2nd combination)
F. Combination of 2 AEDs (additional trials)
G. Combination of 3 AEDs
H. Combination of 3 AEDs (2nd combination)
I. Combination of 3 AEDs (additional trials)
J. Combination of 4 AEDs
K. Combination of 4 AEDS (additional trials)
L. Vagus nerve stimulation (add-on therapy)
M. Ketogenic diet (as monotherapy)
N. Ketogenic diet (as add-on therapy)
O. Evaluation for epilepsy surgery

Step 1 _____
Step 2 _____
Step 3 _____
Step 4 _____
Step 5 _____
Step 6 _____
Step 7 _____

Figure 1. Survey question 1. AED = antiepileptic drug.

Table 3. Pediatric epilepsy survey rating evaluation scale.

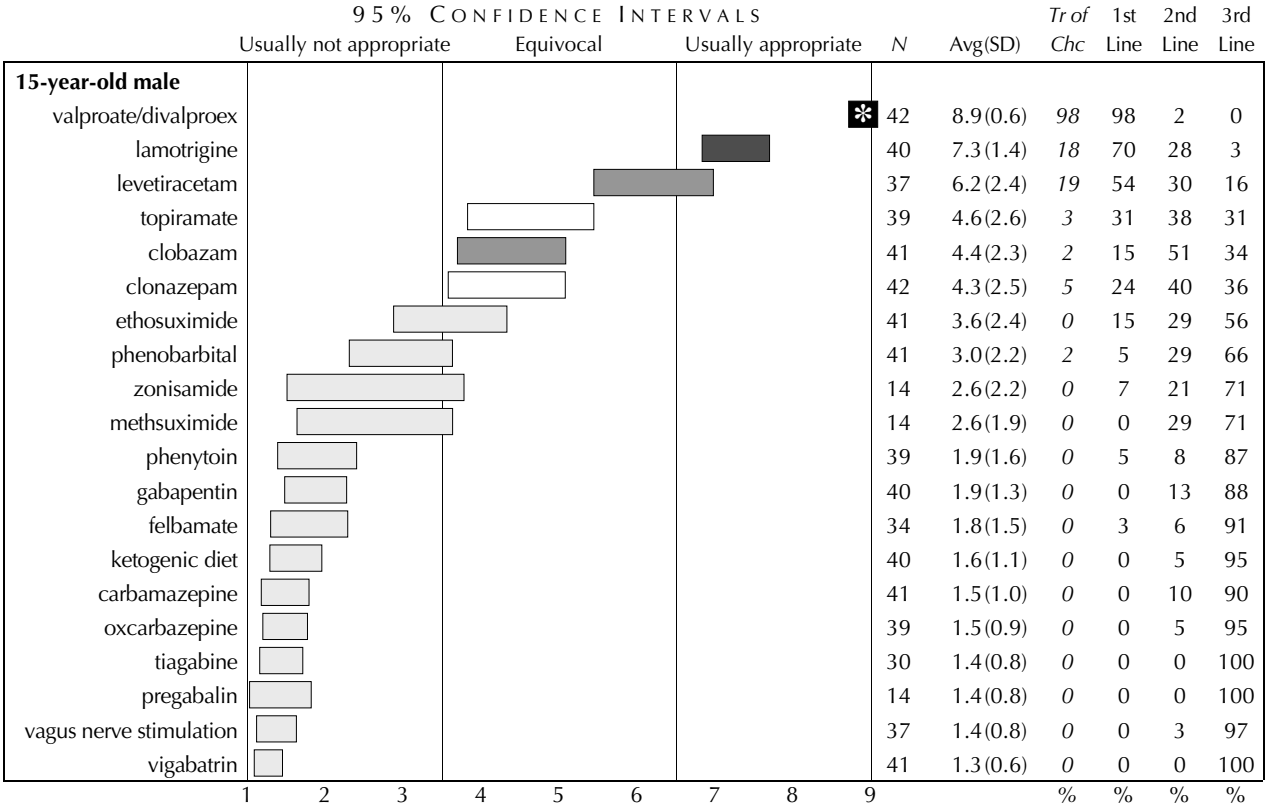
Please evaluate all options; tie scores are permitted; clearly circle a single digit.
9 = Extremely appropriate this is your treatment of choice (may have more than one).
7–8 = Usually appropriate an agent you would often use in this situation.
4–6 = Equivocal an agent you would sometimes use, e.g., if the first choice(s) failed or was contraindicated.
2–3 = Usually inappropriate an agent you would rarely use, or use in special circumstances only.
1 = Extremely inappropriate a treatment that should not be used in this situation.

experts were asked to identify the order in which they would recommend certain therapies. For example, if the monotherapy that was selected as the first step failed, respondents were asked to identify the next best option. This continued until the options were exhausted. Because it was recognized that more than one treatment option might legitimately be considered at any step, "ties" were permitted. *Figure 1* presents an example of one of these overall strategy questions.

The second type of question asked the experts to use a modified 9-point scale (a format developed by the Rand Corporation [Brook *et al.* 1986, Dalkey 1969, Woolfe 1992]) to rate specific treatment choices. The scale was presented to the participants with the instructions shown in Table 3. Figure 2 presents an example of the results of one of these 9-point scale questions. For many of these questions, a "Don't Know" option was included so that the respondents would not feel compelled to rate an option if they did not have knowledge of or experience with it. The results for each question indicate how many experts rated each option.

Not all pediatric epilepsy syndromes could be addressed in the survey; thus the focus was on common pediatric syndromes for which little published information is available regarding sequencing treatment. Experience with previous

Question 33. A ***healthy adolescent*** (male or female) is diagnosed with ***juvenile myoclonic epilepsy***. The patient is being treated for the first time. Assume that you begin with monotherapy. Assume that the parents are amenable to all possible therapies and will be compliant. Please keep in mind the epilepsy syndrome the adolescent has and rate the appropriateness of each of the following treatments.



15-year-old male	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
valproate/divalproex	42	8.9(0.6)	98	98	2	0
lamotrigine	40	7.3(1.4)	18	70	28	3
levetiracetam	37	6.2(2.4)	19	54	30	16
topiramate	39	4.6(2.6)	3	31	38	31
clobazam	41	4.4(2.3)	2	15	51	34
clonazepam	42	4.3(2.5)	5	24	40	36
ethosuximide	41	3.6(2.4)	0	15	29	56
phenobarbital	41	3.0(2.2)	2	5	29	66
zonisamide	14	2.6(2.2)	0	7	21	71
methsuximide	14	2.6(1.9)	0	0	29	71
phenytoin	39	1.9(1.6)	0	5	8	87
gabapentin	40	1.9(1.3)	0	0	13	88
felbamate	34	1.8(1.5)	0	3	6	91
ketogenic diet	40	1.6(1.1)	0	0	5	95
carbamazepine	41	1.5(1.0)	0	0	10	90
oxcarbazepine	39	1.5(0.9)	0	0	5	95
tiagabine	30	1.4(0.8)	0	0	0	100
pregabalin	14	1.4(0.8)	0	0	0	100
vagus nerve stimulation	37	1.4(0.8)	0	0	3	97
vigabatrin	41	1.3(0.6)	0	0	0	100
			%	%	%	%

Figure 2. Survey question 33 results.

surveys of this type in psychiatry has shown that there are a "maximum" number of questions a group of participants will answer (Kahn, personal communication). In other words, a survey could be designed to address a larger group of issues; however, it is unlikely that respondents would be willing to participate in such a survey given the amount of time and effort that would be needed to complete the questionnaire.

Data analysis for options scored on the rating scale

95% confidence interval
For each option, we defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a chi-square test ($p < 0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, and 7–9) (see *table 2*). We calculated the mean, standard deviation, and confidence interval for each option. The confidence interval is calculated statistically and indicates that if the survey were conducted again, there is a 95% chance that the response would fall within this range.

Rating categories
A categorical rating of first, second, or third line was designated for each option based on the lowest category into which its confidence interval fell. Thus, options with a confidence interval that fell entirely at or above 6.5 were assigned a first-line rating, while those with a confidence interval between 3.5 and 6.49 were designated second line, and those with a confidence interval below 3.5 were designated third line. First-, second-, and third-line options were determined for each clinical situation. For items where the bottom of the confidence interval bordered on the next lower category, the item was considered to be in the next lower group. The different rating categories are explained below.

■ "Usually appropriate" or "first line." First-line treatments are those options that the experts identified as extremely or usually appropriate for the given situation (options rated "7, 8, or 9").

* Treatment of choice is a first-line therapy that was rated extremely appropriate ("9") by at least 50% of the experts.

▒ "Equivocal" or "second line." Second-line therapies are reasonable options in instances when the usually appropriate or first-line agent is contraindicated or fails (options rated "4, 5, 6"). Therapy failure can be due to poor efficacy, short- or long-term side effects, or an idiosyncratic reaction.

▒ "Usually not appropriate" or "third line." Third-line therapies are usually not appropriate (for the given scenario); however this is not the same as saying that they should not be used. Instead, these therapies might be considered if other therapies are contraindicated or have already failed to produce complete seizure control.

□ No consensus. A random distribution of responses by chi-square indicates a lack of consensus.

Overview of results

Survey response

The survey was sent to 57 experts, 42 (74%) of whom completed the questionnaire. All the respondents held an M.D. degree. Of the respondents, 12 (29%) were female and 30 (71%) male. Their mean age was 50 years, with a mean of 24 years in practice. Thirty-two (76%) reported spending the majority or all of their time seeing patients, while 7 (17%) reported spending approximately half their time seeing patients. The majority of the experts worked in an academic clinical or research setting. Thirty-nine (93%) of the experts had participated in a research project involving patients with epilepsy during the previous 5 years.

How to read the survey results

For the questions that used the 9-point rating scale, a bar chart depicts the confidence intervals for each item, while a table lists the numeric values for each item (*figure 2*). A number of special graphic conventions are used in the survey results for questions rated on the 9-point scale. A horizontal bar represents the confidence interval for each option. Where the bars for two options do not overlap, there is a statistically significant difference between the mean scores of the two options. "Usually appropriate" or "first-line" therapies are indicated with the darkest shaded bars; "equivocal" or "second-line" items are indicated with medium-shaded bars; "usually not appropriate" or "third-line" confidence interval bars are lightly shaded. An asterisk inside the confidence interval box indicates items that were rated as "treatments of choice" within the first-line category, that is, options that at least 50% of the experts rated as extremely appropriate, or a "9." A clear (unshaded) bar indicates items on which consensus was not reached. A table on the right side of each graphic presents the numeric values for each option: the number of respondents who rated each option, the mean score (Avg), standard deviation (SD), and the percentage of experts who rated the option as treatment of choice, first, second, or third line. For many of the questions, the editors have also provided comments regarding how the data might translate into a treatment recommendation.
Before presenting the recommendations in tabular format, we provide a brief overview of the results and recommen-

dations. The complete data are presented following this summary.

Symptomatic myoclonic and generalized tonic-clonic seizures

We asked about general strategies for treating myoclonic and generalized tonic-clonic seizures in a 2-year-old child with developmental delay and a 12-year-old boy with mental retardation. For a child of any age, the experts recommended beginning with at least two and possibly three trials of monotherapy, before trying at least two or possibly three combinations of 2 antiepileptic drugs. If combination therapy with 2 agents is not effective, the experts would then try a combination of 3 antiepileptic drugs.
Among the available agents, the experts considered valproate the treatment of choice for symptomatic generalized tonic-clonic seizures.

Complex partial seizures

For a healthy child with non-lesional cryptogenic complex partial seizures, the panel recommended two or even three trials of monotherapy before trying one or two trials of a combination of 2 antiepileptic drugs. If these strategies are not successful, the experts would consider an evaluation for epilepsy surgery or additional trials of combinations of 2 or 3 antiepileptic drugs. For a healthy child with mesial temporal sclerosis and complex partial seizures, the experts recommended two to three trials of monotherapy and would then consider a trial of a combination of 2 antiepileptic drugs or an evaluation for epilepsy surgery. The recommendation to consider surgery somewhat earlier in the course of treatment for a child with temporal lobe epilepsy may reflect findings that earlier surgical intervention may result in improved quality of life for the child (see page S20).
For initial monotherapy, the experts recommended carbamazepine and oxcarbazepine as treatments of choice, with valproate also usually appropriate (first line). If carbamazepine or oxcarbazepine was used first and was not efficacious or tolerated, the panel recommended a trial of monotherapy with valproate. If phenytoin was used first and was not efficacious or tolerated, the panel recommended carbamazepine or oxcarbazepine as treatments of choice for the next trial of monotherapy, with valproate another first-line option.

Neonatal seizures

Unlike for status epilepticus in older children, no standard treatment protocols exist for treating neonatal status epilepticus. This lack of data and accepted recommendations is reflected in the experts' ratings, which are fairly evenly divided among different overall treatment strategies. The panel would generally begin with an intravenous (IV), intramuscular (IM), or rectal benzodiazepine or an IV or IM antiepileptic drug. If this was not successful, they would then give a second dose of the same antiepileptic drug or benzodiazepine. If this was not successful, the experts would consider using the benzodiazepine and antiepileptic drug back-to-back or monotherapy with a different IV, IM or rectal benzodiazepine or with a different IV or IM antiepileptic drug. After the seizures have stopped, the panel recommended continuing preventive treatment for 3 to 4 months.
Among the available agents, the experts recommended IV phenobarbital as treatment of choice. If initial treatment with a benzodiazepine failed to control the seizures, the experts recommended IV phenobarbital and IV phenytoin as treatments of choice for the next option.

Infantile spasms

For a healthy 6-month-old with infantile spasms (West syndrome), the experts recommended one to three trials of monotherapy before trying one or more combinations of 2 antiepileptic drugs. Thus the experts strongly endorsed multiple trials of medication before considering an evaluation for epilepsy surgery for the treatment of infantile spasms. In choosing specific medications, the experts recommended vigabatrin as treatment of choice for spasms caused by tuberous sclerosis. For spasms that are symptomatic in etiology, the treatment of choice was also vigabatrin, with adrenocorticotropic hormone (ACTH) and prednisone also usually appropriate.

Lennox-Gastaut syndrome

At least one and possible two trials of monotherapy were recommended for the initial treatment of Lennox-Gastaut syndrome, followed by at least two trials of a combination of 2 antiepileptic drugs if monotherapy fails to control the seizures. Despite findings suggesting that callosotomy and vagus nerve stimulation have efficacy for the treatment of astatic seizures (see page S32), there was only limited support for these options until multiple medication trials have failed.
For initial monotherapy, the experts considered valproate the treatment of choice. If a child did not respond to an initial trial of valproate, lamotrigine is the treatment of choice as the next option, with topiramate another first-line option. If a child does not respond to initial monotherapy with topiramate, the experts recommended valproate as the treatment of choice, with lamotrigine another first-line option. If the child was initially treated with lamotrigine and did not respond, valproate was treatment of choice for the next option, with topiramate another first-line option.

Febrile seizures

Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or cluster of febrile seizures (note that rectal diazepam does not have formal approval from the U.S. FDA for treatment of febrile seizures or prolonged seizures in children under 2 years of age). Valproate received first-line ratings as preventive treatment for febrile seizures. Note, however, that concerns have been expressed about the risks and potential side effects of using medication to prevent future febrile seizures, so that such preventive use was not recommended by the 1999 American Academy of Pediatrics Practice Parameter (American Academy of Pediatrics 1999) and the Scottish Intercollegiate Guidelines Network (2005).

Benign childhood epilepsy with centro-temporal spikes

Valproate was the treatment of choice for benign childhood epilepsy with centro-temporal spikes. Gabapentin and sulthiame are the only two medications that have been evaluated for treatment of benign childhood epilepsy with centro-temporal spikes in randomized clinical trials. However, neither of these medications was endorsed by the experts as a first- or second-line option.

Absence epilepsy

Valproate was rated as treatment of choice and lamotrigine was another first-line option for both childhood and juvenile absence epilepsy. Ethosuximide was another first-line option for childhood absence epilepsy. If initial treatment with ethosuximide failed in childhood absence epilepsy, then the experts considered valproate treatment of choice and lamotrigine another first-line treatment as the next option. If initial treatment with valproate failed in juvenile absence epilepsy, then the experts considered lamotrigine as treatment of choice for the next option.

Juvenile myoclonic epilepsy

For juvenile myoclonic epilepsy in adolescent males, valproate was treatment of choice, with lamotrigine another first-line option; for juvenile myoclonic epilepsy in adolescent females, lamotrigine was treatment of choice, with valproate another first-line option.

Newly diagnosed epilepsy in the emergency department

Valproate was considered treatment of choice for a 6-year-old child with new onset seizures, probably reflecting the view that valproate is currently the antiepileptic drug with the broadest spectrum of efficacy across all types of seizures.

Status epilepticus

The experts recommended an IV, IM, or rectal benzodiazepine as initial treatment for a child with convulsive status epilepticus. The next step the panel recommended is to give a second dose of the same or a different benzodiazepine. If these strategies do not work, the experts would either give a benzodiazepine and an IV antiepileptic drug back-to-back or use monotherapy with an IV or IM antiepileptic drug. If this did not work, they would give another dose of the same or a different antiepileptic drug. If none of these strategies worked, the experts would then consider using an iatrogenic drug coma.
In selecting specific agents, the experts rated IV diazepam as treatment of choice for initial therapy for generalized tonic-clonic, absence, and complex partial status epilepticus. Rectal diazepam and IV lorazepam were other treatments of choice for generalized tonic-clonic status epilepticus, while IV lorazepam was also considered usually appropriate (first line) for complex partial status epilepticus.

1. Symptomatic myoclonic and generalized tonic-clonic seizures

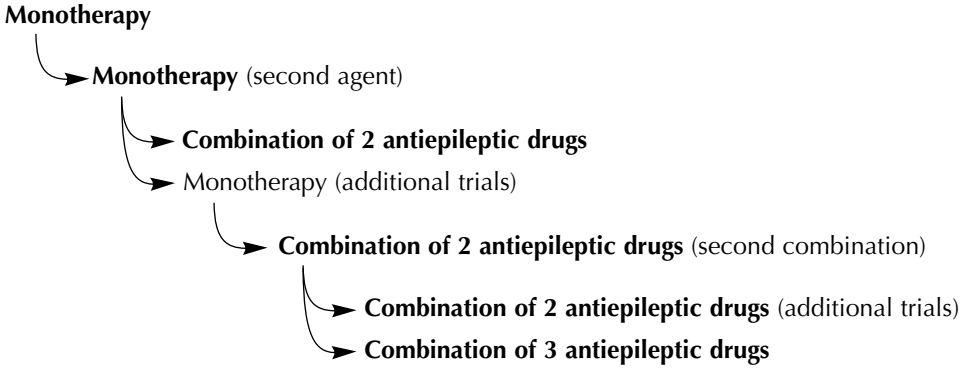
1A. Overall strategy

Question 1. A healthy 2-year-old child with developmental delay is diagnosed with ***myoclonic and generalized tonic-clonic seizures*** and has not been treated yet. Assume the family is amenable to all possible therapies and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated. For each step, you may list more than one treatment if there are treatment approaches that you consider equivalent; however, you may list each treatment only once.

		n for each step							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	40	40							1.00
Monotherapy 2nd agent	29		28	1					2.03
Combination of 2 AEDs	40		14	22	4				2.75
Monotherapy (additional trials)	8			7	1				3.13
Combination of 2 AEDs (2nd combination)	33			12	18	2	1		3.76
Combination of 2 AEDs (additional trials)	22				9	10	2	1	4.77
Ketogenic diet (as monotherapy)	3			1		1		1	5.00
Combination of 3 AEDs	33				4	16	11	2	5.33
Evaluation for epilepsy surgery	19				5	3	3	8	5.74
Combination of 4 AEDs	6					2	2	2	6.00
Ketogenic diet (as add-on therapy)	25			2		4	8	11	6.04
Vagus verve stimulation (add-on therapy)	10				1	1	4	4	6.10
Combination of 3 AEDs (2nd combination)	16					3	7	6	6.19
Combination of 4 AEDS (additional trials)	2						1	1	6.50
Combination of 3 AEDs (additional trials)	5						1	4	6.80

AED = antiepileptic drug.

Comment: there are two ways to analyze these results: 1) "across the row" or 2) "down the column." The first analysis looks at each therapy and generates an overall "average" using the step number multiplied by the number of times the therapeutic option was chosen at that step divided by the number of experts who rated the option. This average is listed in the right-hand column. The second analysis examines each step to determine which therapies appear most often at that decision point. For example, at step 1, all of the 40 experts who responded supported a trial of monotherapy; at step 2, 67% (28/42) of the responses supported a second trial of monotherapy, although 33% (14/42 of the responses) favored a combination of 2 antiepileptic drugs. At step 3, the experts favored a combination of 2 antiepileptic drugs (34/45 of the responses, 76%) over further trials of monotherapy (8/45 responses, 18%). At step 4, three quarters of the responses (31/42, 74%) supported use of 2 antiepileptic drugs. At step 5, the experts endorsed further medication trials, although there was a small amount of support (12% of the responses, 5/42) for the ketogenic diet. Evaluation for epilepsy surgery was first supported at step 4 but was endorsed by fewer than 20% of the responses until step 7. Ketogenic diet was first supported at step 3 and vagus nerve stimulation at step 4, but there was little support for their use except as a last option. Few experts recommended combinations of 4 antiepileptic drugs as a therapeutic option.

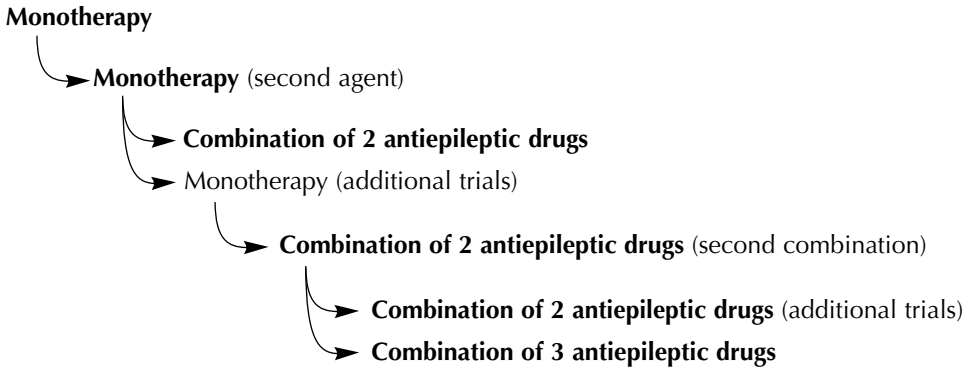


Question 2. A 12-year-old male with mental retardation is diagnosed with ***myoclonic and generalized tonic-clonic seizures*** and has not been treated yet. Assume the patient and family are willing to accept all possible therapies and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated. For each step, you may list more than one treatment if there are treatment approaches that you consider equivalent; however, you may list each treatment only once.

		n for each step							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	40	40							1.00
Monotherapy 2nd agent	34		34						2.00
Combination of 2 AEDs	40		7	28	5				2.95
Monotherapy (additional trials)	9			7	1		1		3.44
Combination of 2 AEDs (2nd combination)	29			6	16	6	1		4.07
Ketogenic diet (as monotherapy)	2				1	1			4.50
Combination of 2 AEDs (additional trials)	23				6	13	3	1	4.96
Combination of 3 AEDs	31			2	6	6	15	2	5.29
Combination of 4 AEDs	5				2		1	2	5.60
Evaluation for epilepsy surgery	17				3	5	2	7	5.76
Ketogenic diet (as add-on therapy)	20				1	7	4	8	5.95
Combination of 3 AEDs (additional trials)	3					1	1	1	6.00
Combination of 3 AEDs (2nd combination)	17				1	3	7	6	6.06
Combination of 4 AEDS (additional trials)	4					1		3	6.50
Vagus nerve stimulation (add-on therapy)	18				1		6	11	6.50

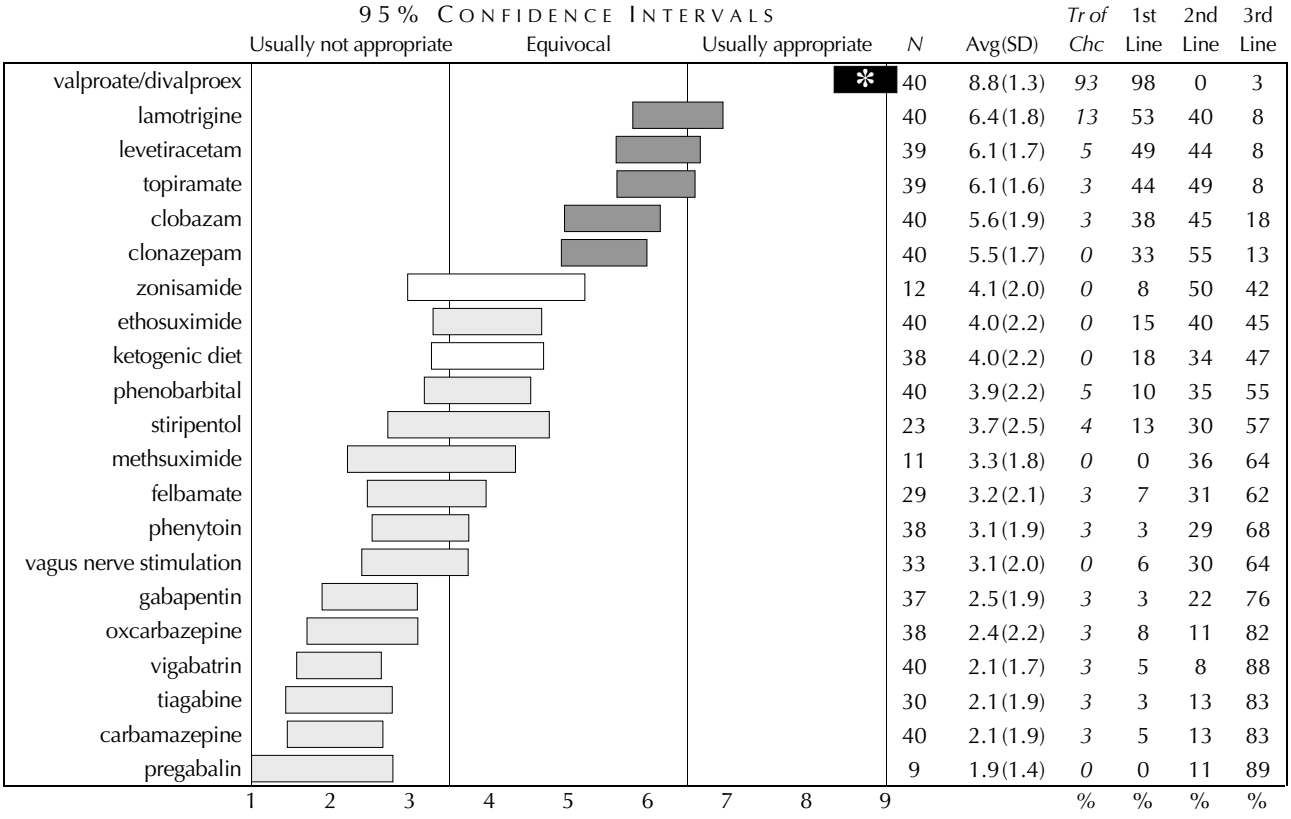
AED = antiepileptic drug.

Comment: the recommendations for a 12-year-old with mental retardation are almost exactly the same as for the 2-year-old described in question 1. Few experts recommended combinations of 4 antiepileptic drugs as a therapeutic option, and vagus nerve stimulation was seen as a last option. As in question 1, there was limited support for nonpharmacologic strategies (e.g., surgery, ketogenic diet, vagus nerve stimulation) until the patient had failed to respond to multiple trials of medication.



1B. Treatment selection for myoclonic and generalized tonic-clonic seizures: survey results

Question 10. A healthy 2-year-old child with developmental delay is diagnosed with ***myoclonic and generalized tonic-clonic seizures***. The child is starting therapy for the first time. Assume you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Please keep in mind the dominant seizure type that the child is experiencing and rate the appropriateness of each of the following treatments.



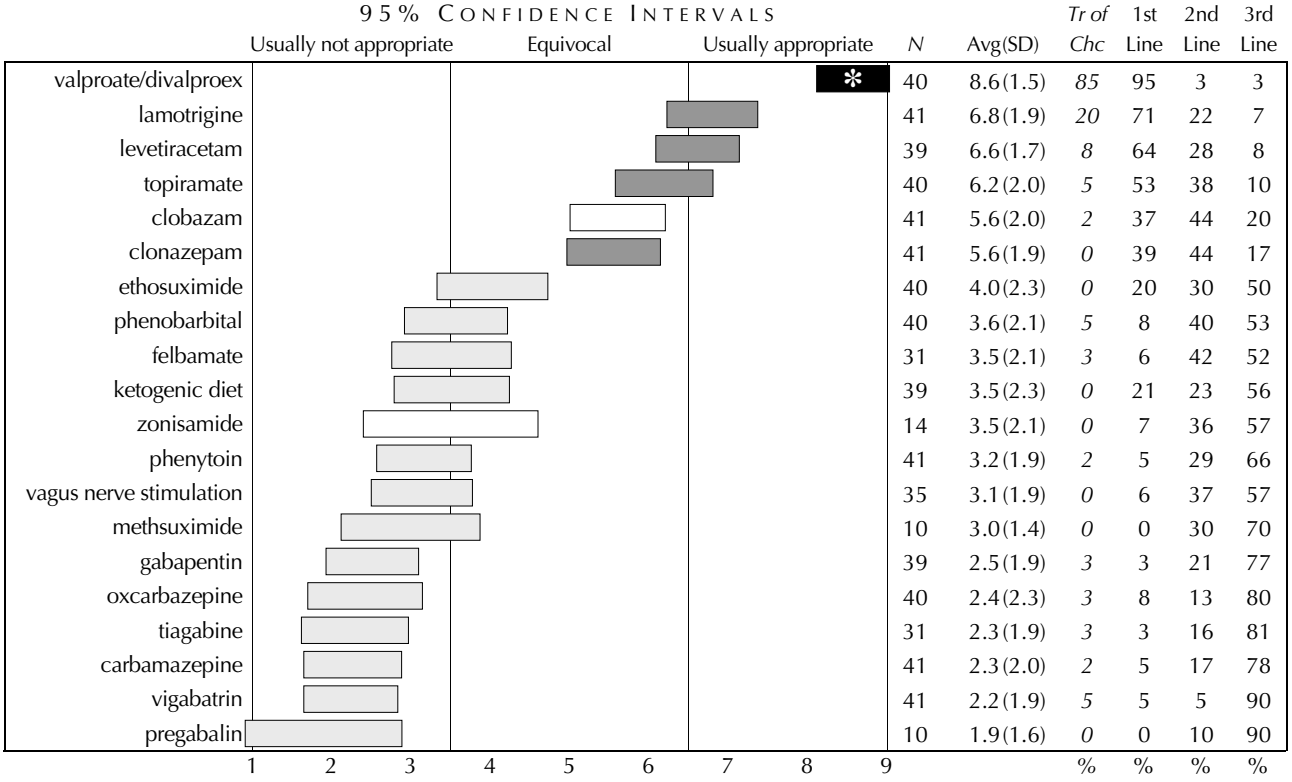
	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
valproate/divalproex	40	8.8(1.3)	*93*	98	0	3
lamotrigine	40	6.4(1.8)	*13*	53	40	8
levetiracetam	39	6.1(1.7)	*5*	49	44	8
topiramate	39	6.1(1.6)	*3*	44	49	8
clobazam	40	5.6(1.9)	*3*	38	45	18
clonazepam	40	5.5(1.7)	*0*	33	55	13
zonisamide	12	4.1(2.0)	*0*	8	50	42
ethosuximide	40	4.0(2.2)	*0*	15	40	45
ketogenic diet	38	4.0(2.2)	*0*	18	34	47
phenobarbital	40	3.9(2.2)	*5*	10	35	55
stiripentol	23	3.7(2.5)	*4*	13	30	57
methsuximide	11	3.3(1.8)	*0*	0	36	64
felbamate	29	3.2(2.1)	*3*	7	31	62
phenytoin	38	3.1(1.9)	*3*	3	29	68
vagus nerve stimulation	33	3.1(2.0)	*0*	6	30	64
gabapentin	37	2.5(1.9)	*3*	3	22	76
oxcarbazepine	38	2.4(2.2)	*3*	8	11	82
vigabatrin	40	2.1(1.7)	*3*	5	8	88
tiagabine	30	2.1(1.9)	*3*	3	13	83
carbamazepine	40	2.1(1.9)	*3*	5	13	83
pregabalin	9	1.9(1.4)	*0*	0	11	89
			%	%	%	%

Comment: even with the risk of hepatotoxicity, valproate is still rated as treatment of choice (extremely appropriate) for convulsive seizures in a 2-year-old child with developmental delay just as it is for a healthy normal adult or adolescent with convulsive seizures (Bourgeois 2003, Cowling *et al.* 2007, Faught 2007, Karceski *et al.* 2001 and 2005). Ratings for lamotrigine were equivocal (high second-line), possibly reflecting reports that it may aggravate myoclonic seizures (Carrazana and Wheeler 2001, Crespel *et al.* 2005, Guerrini *et al.* 1998). Another option that received equivocal (high second-line) ratings was levetiracetam, possibly reflecting its structural similarity to the anti-myoclonic agent piracetam and clinical experience (Wheless and Bourgeois 2004). Topiramate was another option that received equivocal (high second line) ratings. Clinical trials of topiramate in children over 2 years of age have been completed (Biton *et al.* 1999, Wheless 2000), and it has been approved by the U.S. Food and Drug Administration for use as adjunctive therapy in this age group (Topamax package insert 2005). Historically, benzodiazepines (primarily clonazepam) and valproate have been used to treat myoclonic seizures based on clinical experience (Sankar *et al.* 2005, Wheless 2003). This probably accounts for the second-line ratings received by clobazam and clonazepam. Although the ketogenic diet was originally used in the treatment of myoclonic seizures (Wheless *et al.* 2001), there was no consensus among the experts on its role here.

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

Question 11. A healthy 12-year-old male with mental retardation is diagnosed with ***myoclonic and generalized tonic-clonic seizures***. The child is starting therapy for the first time. Assume you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
valproate/divalproex	40	8.6(1.5)	*85*	95	3	3
lamotrigine	41	6.8(1.9)	*20*	71	22	*7*
levetiracetam	39	6.6(1.7)	*8*	64	28	8
topiramate	40	6.2(2.0)	*5*	53	38	10
clobazam	41	5.6(2.0)	*2*	37	44	20
clonazepam	41	5.6(1.9)	*0*	39	44	17
ethosuximide	40	4.0(2.3)	*0*	20	30	50
phenobarbital	40	3.6(2.1)	*5*	8	40	53
felbamate	31	3.5(2.1)	*3*	6	42	52
ketogenic diet	39	3.5(2.3)	*0*	21	23	56
zonisamide	14	3.5(2.1)	*0*	7	36	57
phenytoin	41	3.2(1.9)	*2*	5	29	66
vagus nerve stimulation	35	3.1(1.9)	*0*	6	37	57
methsuximide	10	3.0(1.4)	*0*	0	30	70
gabapentin	39	2.5(1.9)	*3*	3	21	77
oxcarbazepine	40	2.4(2.3)	*3*	8	13	80
tiagabine	31	2.3(1.9)	*3*	3	16	81
carbamazepine	41	2.3(2.0)	*2*	5	17	78
vigabatrin	41	2.2(1.9)	*5*	5	5	90
pregabalin	10	1.9(1.6)	*0*	0	10	90
			%	%	%	%

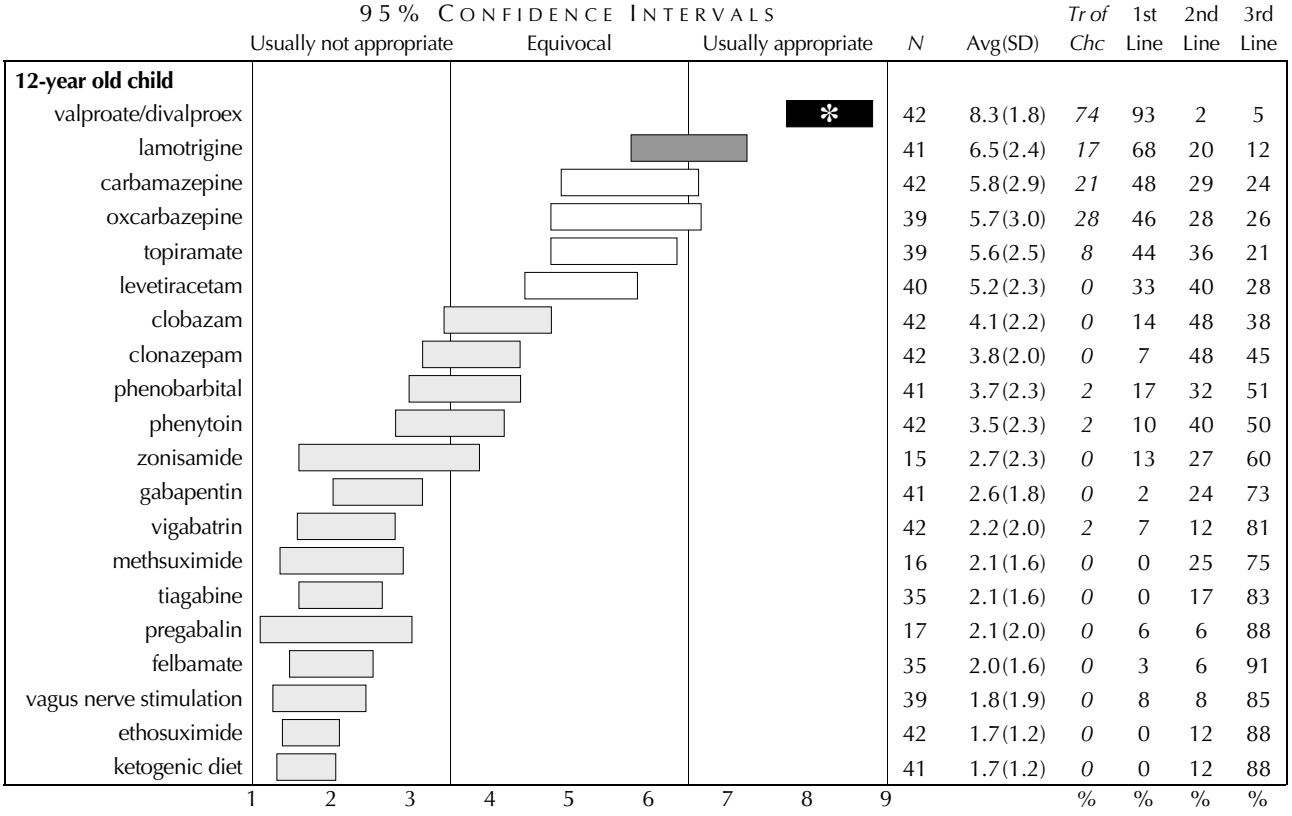
Comment: as initial therapy for a healthy 12-year-old with mental retardation diagnosed with myoclonic and generalized tonic-clonic seizures, valproate was treatment of choice. This opinion is consistent with a recent review concerning the use of valproate in children conducted by experts on epilepsy at a workshop in Goteborg (Aldenkamp *et al.* 2006). Lamotrigine, levetiracetam, and topiramate received equivocal (high second-line) ratings. Valproate, topiramate, and lamotrigine have historically been considered broad spectrum antiepileptic drugs, a role confirmed here by the experts for convulsive seizures. Levetiracetam has also emerged as a potential broad spectrum antiepileptic drug (Berkovic *et al.* 2007, Glauser and Dulac 2003, Glauser and Pellock 2002, Verdu *et al.* 2005, Wheless and Bourgeois 2004). The use of felbamate as a broad spectrum antiepileptic drug is limited due to concerns about potential hepatic or hematopoietic toxicity (Pellock 1999b, Pellock *et al.* 2006).

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

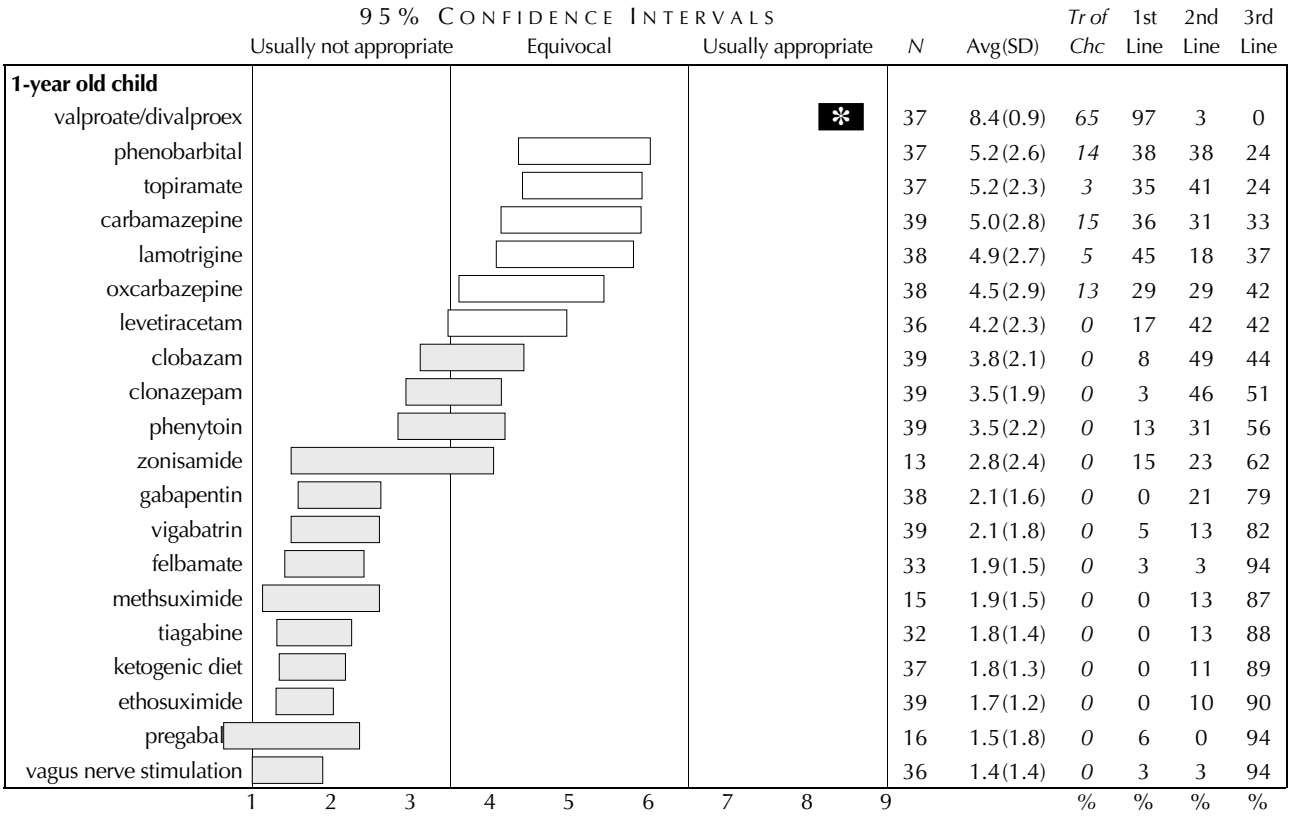
1C. Treatment selection for symptomatic generalized tonic-clonic seizures: survey results

Question 30. A healthy child (age 1 year or age 12 years) is newly diagnosed with ***symptomatic generalized tonic-clonic seizures***. The child is starting therapy for the first time. Assume you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Please rate the appropriateness of each of the following treatments.



Comment: as initial therapy for an older child with symptomatic generalized tonic-clonic seizures, valproate was the treatment of choice, with lamotrigine a high second-line choice. This is similar to the first-line recommendations for an adult with symptomatic generalized tonic-clonic seizures (Karceski *et al.* 2005). There was a lack of agreement (i.e., no consensus and wide confidence intervals) concerning the role of carbamazepine, oxcarbazepine, topiramate, and levetiracetam. The favorable ratings given to carbamazepine and oxcarbazepine by some of the experts may reflect the belief that some symptomatic generalized seizures represent partial seizures with secondary generalization (Giroud *et al.* 1993, Theodore *et al.* 1994) as well as results of studies that have shown that these two agents have efficacy for the treatment of generalized seizures (Christe *et al.* 1997, Guerreiro *et al.* 1997, Prasad *et al.* 2003).

Question 30. *Continued*



Comment: just as with the older child, valproate is the treatment of choice for a younger child with symptomatic generalized tonic-clonic seizures. There was no consensus on many other commonly used medications, such as phenobarbital, topiramate, carbamazepine, lamotrigine, oxcarbazepine, and levetiracetam. These results probably reflect the fact that no controlled studies have been done in patients of this age with symptomatic generalized tonic-clonic seizures, resulting in confusion about what antiepileptic drug works. Some of the experts may have rated a drug lower because there are no research data concerning it and so their ratings reflect their experience (i.e., poor clinical results), while some of the experts may have rated a drug higher, again probably reflecting their results (i.e., a good experience with the drug).

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

1D. Medication recommendations for myoclonic and generalized tonic-clonic seizures

Unfortunately, to date, no clinical trials (either registry or comparative) have been done on the treatment of symptomatic generalized tonic-clonic seizures (with or without myoclonic seizures) in children. Nevertheless, this is a common clinical scenario in this population so that this expert advice can help guide clinical care until formal studies are performed. The experts considered valproate the treatment of choice for symptomatic generalized tonic-clonic seizures.

Clinical presentation	Patient	Usually appropriate	Sometimes appropriate*
Myoclonic and generalized tonic-clonic seizures	Healthy 2-year old child with developmental delay or healthy 12-year old boy with mental retardation	***Valproate***	Lamotrigine Levetiracetam Topiramate
Symptomatic generalized tonic-clonic seizures	Healthy 1-year old child	***Valproate***	—
	Healthy 12-year old child	***Valproate***	Lamotrigine

*Equivocal but high second-line ratings
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

2. Complex partial seizures

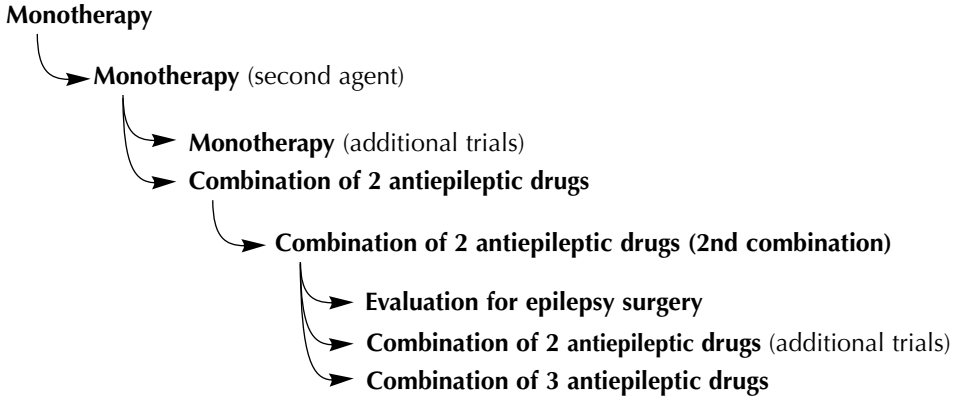
2A. Overall strategy

Question 8. A healthy 8-year old child is diagnosed with ***non-lesional cryptogenic complex partial seizures*** and has not been treated yet. Assume the parents are amenable to all possible therapies and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

		n for each step							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	40	40							1.00
Monotherapy 2nd agent	38		38						2.00
Monotherapy (additional trials)	18			17	1				3.06
Combination of 2 AEDs	40		3	20	14	3			3.43
Combination of 2 AEDs (2nd combination)	36			2	15	16	3		4.56
Evaluation for epilepsy surgery	33		1	2	8	6	9	7	5.24
Combination of 2 AEDs (additional trials)	26				1	9	12	4	5.73
Combination of 3 AEDs	24			2	2	6	3	11	5.79
Ketogenic diet (as add-on therapy)	11			1		2	5	3	5.82
Combination of 4 AEDs	6				1	1	1	3	6.00
Combination of 3 AEDs (2nd combination)	7					1	4	2	6.14
Ketogenic diet (as monotherapy)	2						1	1	6.50
Vagus nerve stimulation (add-on therapy)	13					1	3	9	6.62
Combination of 3 AEDs (additional trials)	4						1	3	6.75
Combination of 4 AEDS (additional trials)	1							1	7.00

AED = antiepileptic drug.

Comment: at step 1, all of the 40 experts who responded supported a trial of monotherapy. If this was not successful, 38 (90%) of the 42 responses favored trying a different agent as monotherapy for step 2. At step 3, 50% (22/44) of the responses endorsed a combination of 2 antiepileptic drugs, while 39% of the responses (17/44) endorsed a third trial of monotherapy. At step 4, the majority of the responses (71%, 30/42) endorsed a combination of 2 antiepileptic drugs. The recommendation to use additional monotherapy trials before trying polytherapy is similar to the recommendation from the National French epilepsy survey in adults (Semah *et al.* 2004). Although no pediatric studies have assessed whether alternative monotherapy is superior to combination therapy with 2 antiepileptic drugs, the adult literature from observational studies suggests no difference in efficacy or discontinuation due to adverse effects between these two choices after failure of the initial monotherapy (Mohanraj and Brodie 2005). At steps 4 and 5, a number of the responses supported an evaluation for epilepsy surgery (19% at step 4 and 13% at step 5) , which is consistent with Japanese clinical experience showing that only rare children who have partial-onset seizures become seizure-free with medication treatment after the failure of four to five medications (Aso and Watanabe 2000).

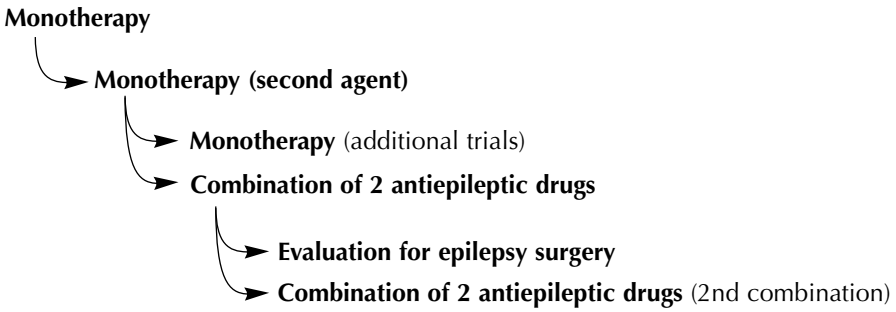


Question 9. A healthy 9-year-old child has ***right-sided mesial temporal sclerosis and complex partial seizures*** and has not been treated yet. Assume the parents are amenable to all possible therapies and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

		***n* for each step**							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	40	39	1						1.03
Monotherapy 2nd agent	36		32	4					2.11
Monotherapy (additional trials)	17			11	6				3.35
Combination of 2 AEDs	39		5	16	9	9			3.56
Evaluation for epilepsy surgery	38	1	4	8	12	7	3	3	4.08
Combination of 2 AEDs (2nd combination)	35			4	10	11	10		4.77
Combination of 3 AEDs	19			1	3	4	8	3	5.47
Combination of 4 AEDs	6				1	1	2	2	5.83
Combination of 3 AEDs (2nd combination)	8				1	2	1	4	6.00
Combination of 4 AEDS (additional trials)	2					1		1	6.00
Combination of 2 AEDs (additional trials)	21				2	4	5	10	6.10
Ketogenic diet (as add-on therapy)	10					2	5	3	6.10
Combination of 3 AEDs (additional trials)	5						3	2	6.40
Vagus nerve stimulation (add-on therapy)	10				1		3	6	6.40
Ketogenic diet (as monotherapy)	1							1	7.00

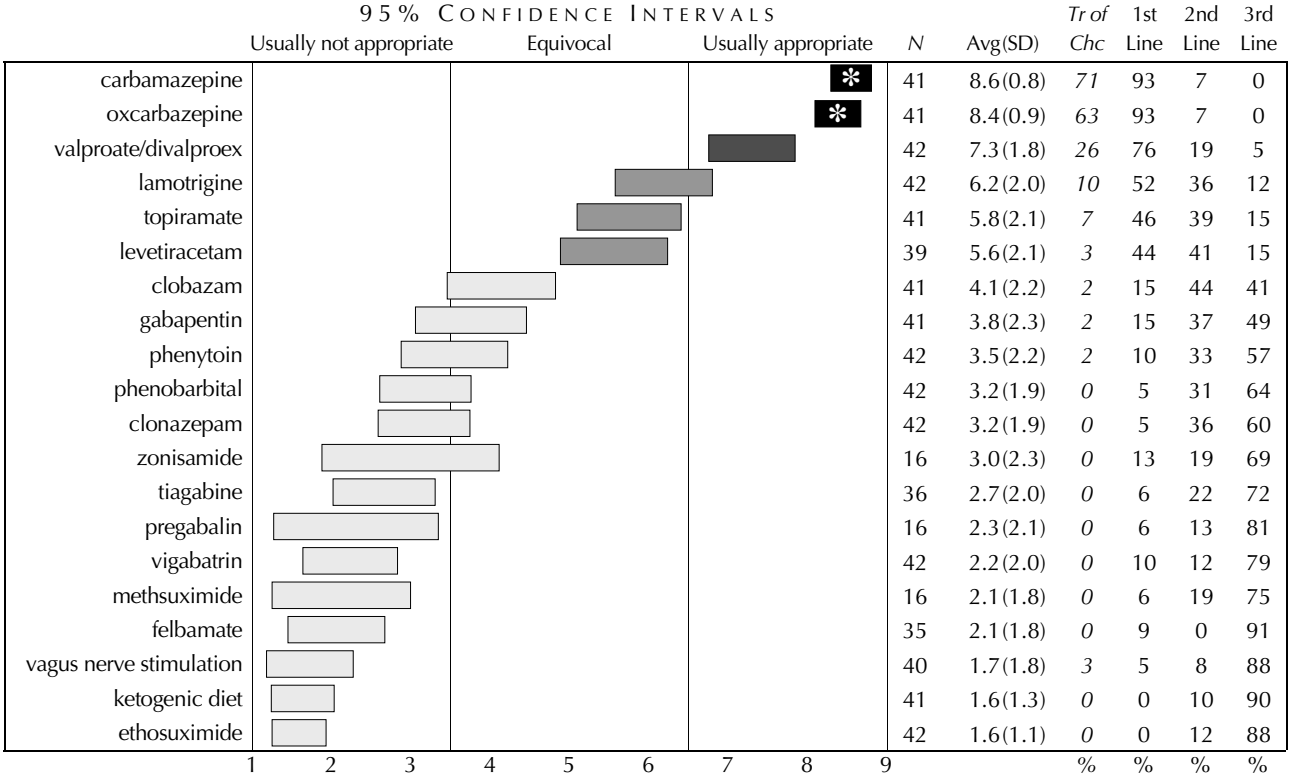
AED = antiepileptic drug.

Comment: at step 1, 98% (39/40) of the responses supported a trial of monotherapy. At step 2, 76% (32/42) of the responses endorsed a second trial of monotherapy. At step 3, the experts were divided as to the next best strategy, with 45% (20/44) of the responses supporting a trial of 2 antiepileptic drugs, 34% (15/44) additional trials of monotherapy, and 18% (8/44) an evaluation for epilepsy surgery. At step 4, 42% (19/45) of the responses support a combination of 2 antiepileptic drugs, while 27% (12/45) of the responses supported an evaluation for epilepsy surgery. Children and adults with mesial temporal sclerosis typically have pharmacoresistant epilepsy (Dlugos *et al.* 2001, Semah *et al.* 1998, Spencer 2002). The recommendation to evaluate the child with mesial temporal sclerosis for epilepsy surgery after the failure of appropriate trials of antiepileptic drugs is consistent with the recent practice parameter of the American Academy of Neurology, American Epilepsy Society, and the American Association of Neurological Surgeons (Engel *et al.* 2003). Surgery for temporal-lobe epilepsy results in fewer seizures and improved quality of life compared with ongoing medical therapy (Spencer 2002, Wiebe *et al.* 2001). Interestingly, both the 2001 and 2005 expert consensus surveys on the treatment of epilepsy in adults suggested an evaluation for epilepsy surgery as the fourth step for patients with mesial temporal sclerosis (Karceski *et al.* 2001 and 2005). The recommendation of some of the experts to consider a surgical evaluation earlier in the treatment of children may reflect the belief that performing epilepsy surgery in childhood, rather than waiting for adulthood, results in an improved quality of life for the child (Duchowny *et al.* 1992, Erba *et al.* 1992, Mizrahi *et al.* 1990, Sinclair *et al.* 2003). In addition, recent studies show a greater functional recovery after temporal lobe surgery in childhood compared with adults (Gleissner *et al.* 2005).



2B. Treatment selection for cryptogenic complex partial seizures: survey results

Question 31. A healthy, cognitively, and neurologically normal 6-year-old child is diagnosed with ***cryptogenic complex partial seizures***. The patient is starting therapy for the first time. Assume you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Please rate the appropriateness of each of the following treatments.

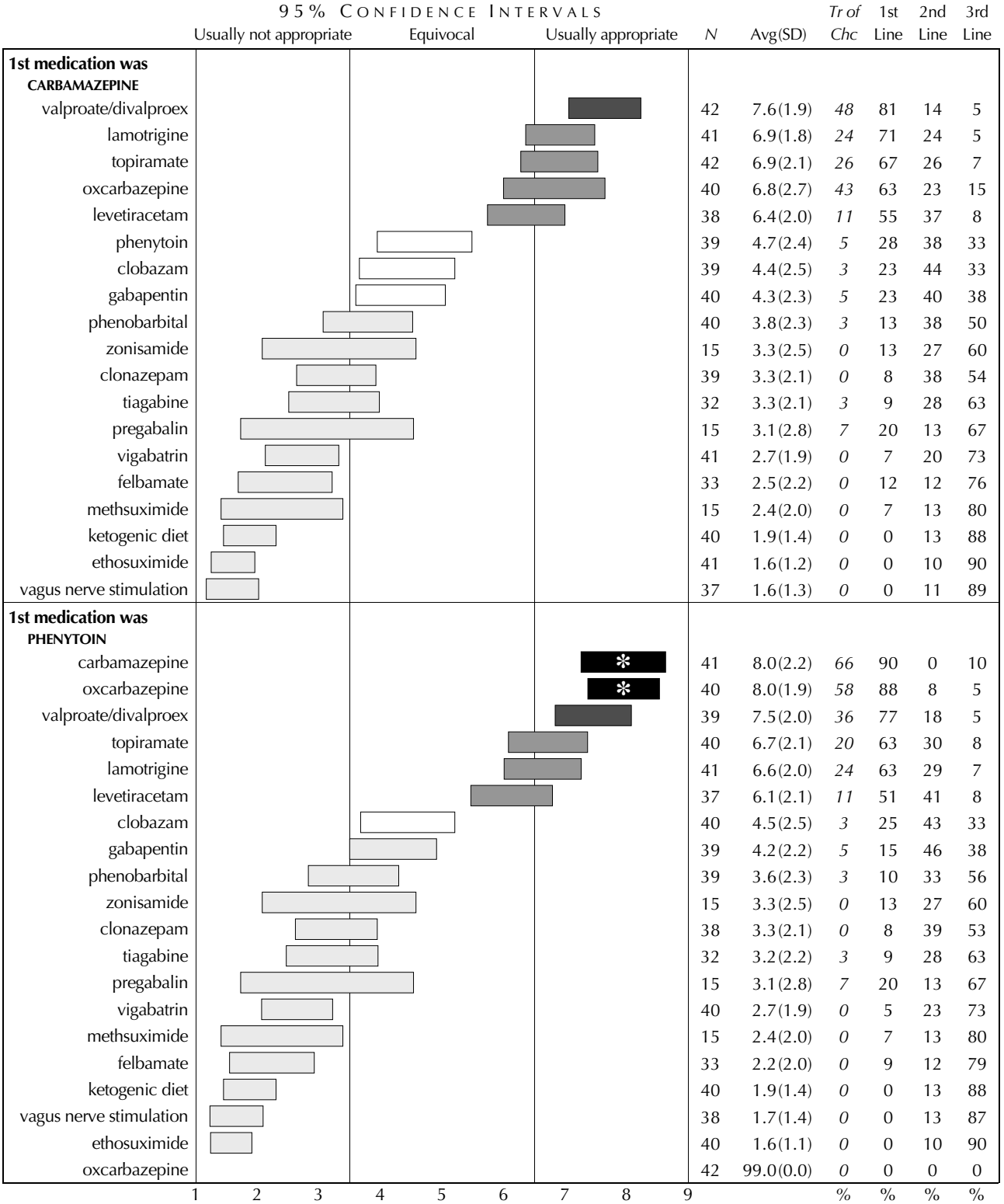


Comment: as initial therapy, carbamazepine and oxcarbazepine were considered treatments of choice (extremely appropriate); valproate was the only other usually appropriate (first-line) option; and lamotrigine was considered sometimes appropriate (equivocal but high second line) with topiramate and levetiracetam other second-line options for a child with complex partial seizures. These findings agree with results of the recent Study of Standard and New Antiepileptic Drugs (SANAD), which showed that for time to 12-month remission, carbamazepine (chosen as standard treatment) was significantly better than gabapentin and had a non-significant advantage over lamotrigine, topiramate, and oxcarbazepine (Marson *et al.* 2007a). Comparing these results to those for adults, we note that, in the 2001 survey, carbamazepine was treatment of choice and oxcarbazepine another first-line option for adults with complex partial seizures (Karceski *et al.* 2001); however, in the 2005 survey, carbamazepine, oxcarbazepine, and lamotrigine were all rated as treatments of choice for an adult or adolescent with complex partial seizures (Karceski *et al.* 2005). Phenytoin, one of the most prescribed medications in the United States (Pfizer data on file), received third-line (usually not appropriate) ratings, probably due to concerns over potential cosmetic side effects (Scheinfeld 2004). Phenobarbital is the most widely prescribed antiepileptic drug worldwide. Evidence from randomized trials or observational studies consistently show that phenobarbital has overall efficacy similar to other established antiepileptic drugs (e.g., phenytoin and carbamazepine) (Brodie and Kwan 2004, Kwan and Brodie 2004b). However, the perception of phenobarbital as a highly neurotoxic compound may have resulted in it receiving a third-line rating from the experts. The two highest rated treatment choices for children with complex partial seizures (carbamazepine and oxcarbazepine) were also considered first choices for adult males in France (Semah *et al.* 2004).

Key

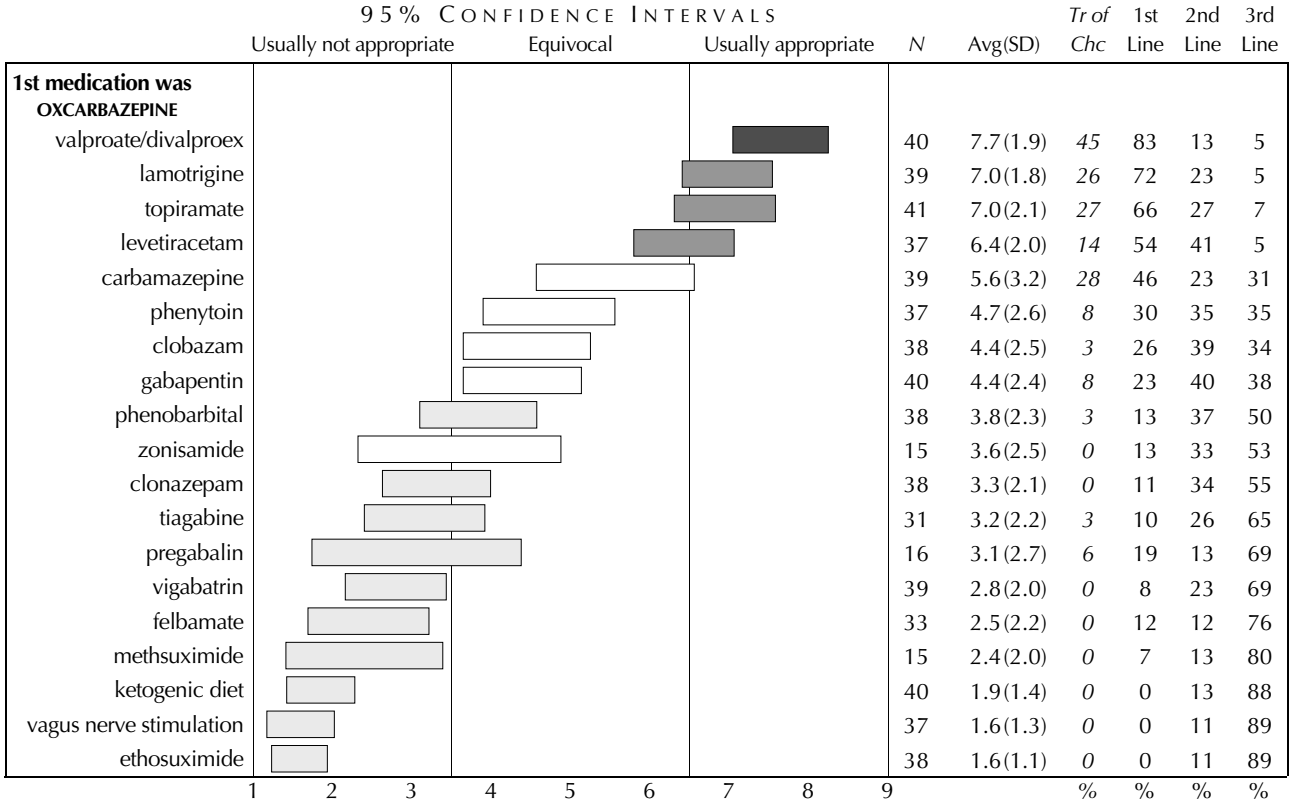
- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

Question 32. Second monotherapy. Assume the first treatment you choose is carbamazepine, phenytoin, or oxcarbazepine. The child has no reduction of seizures or a limited response or the drug was poorly tolerated. Assume you would next choose a second monotherapy trial. Rate the appropriateness of each of the following treatments as a second monotherapy.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
1st medication was CARBAMAZEPINE						
valproate/divalproex	42	7.6(1.9)	*48*	81	14	5
lamotrigine	41	6.9(1.8)	*24*	71	24	5
topiramate	42	6.9(2.1)	*26*	67	26	7
oxcarbazepine	40	6.8(2.7)	*43*	63	23	15
levetiracetam	38	6.4(2.0)	*11*	55	37	8
phenytoin	39	4.7(2.4)	*5*	28	38	33
clobazam	39	4.4(2.5)	*3*	23	44	33
gabapentin	40	4.3(2.3)	*5*	23	40	38
phenobarbital	40	3.8(2.3)	*3*	13	38	50
zonisamide	15	3.3(2.5)	*0*	13	27	60
clonazepam	39	3.3(2.1)	*0*	8	38	54
tiagabine	32	3.3(2.1)	*3*	9	28	63
pregabalin	15	3.1(2.8)	*7*	20	13	67
vigabatrin	41	2.7(1.9)	*0*	7	20	73
felbamate	33	2.5(2.2)	*0*	12	12	76
methsuximide	15	2.4(2.0)	*0*	7	13	80
ketogenic diet	40	1.9(1.4)	*0*	0	13	88
ethosuximide	41	1.6(1.2)	*0*	0	10	90
vagus nerve stimulation	37	1.6(1.3)	*0*	0	11	89
1st medication was PHENYTOIN						
carbamazepine	41	8.0(2.2)	*66*	90	0	10
oxcarbazepine	40	8.0(1.9)	*58*	88	8	5
valproate/divalproex	39	7.5(2.0)	*36*	77	18	5
topiramate	40	6.7(2.1)	*20*	63	30	8
lamotrigine	41	6.6(2.0)	*24*	63	29	7
levetiracetam	37	6.1(2.1)	*11*	51	41	8
clobazam	40	4.5(2.5)	*3*	25	43	33
gabapentin	39	4.2(2.2)	*5*	15	46	38
phenobarbital	39	3.6(2.3)	*3*	10	33	56
zonisamide	15	3.3(2.5)	*0*	13	27	60
clonazepam	38	3.3(2.1)	*0*	8	39	53
tiagabine	32	3.2(2.2)	*3*	9	28	63
pregabalin	15	3.1(2.8)	*7*	20	13	67
vigabatrin	40	2.7(1.9)	*0*	5	23	73
methsuximide	15	2.4(2.0)	*0*	7	13	80
felbamate	33	2.2(2.0)	*0*	9	12	79
ketogenic diet	40	1.9(1.4)	*0*	0	13	88
vagus nerve stimulation	38	1.7(1.4)	*0*	0	13	87
ethosuximide	40	1.6(1.1)	*0*	0	10	90
oxcarbazepine	42	99.0(0.0)	*0*	0	0	0
			%	%	%	%

Question 32. *Continued*



1st medication was	*N*	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
OXCARBAZEPINE						
valproate/divalproex	40	7.7(1.9)	*45*	83	13	5
lamotrigine	39	7.0(1.8)	*26*	72	23	5
topiramate	41	7.0(2.1)	*27*	66	27	*7*
levetiracetam	37	6.4(2.0)	*14*	54	41	5
carbamazepine	39	5.6(3.2)	*28*	46	23	31
phenytoin	37	4.7(2.6)	*8*	30	35	35
clobazam	38	4.4(2.5)	*3*	26	39	34
gabapentin	40	4.4(2.4)	*8*	23	40	38
phenobarbital	38	3.8(2.3)	*3*	13	37	50
zonisamide	15	3.6(2.5)	*0*	13	33	53
clonazepam	38	3.3(2.1)	*0*	11	34	55
tiagabine	31	3.2(2.2)	*3*	10	26	65
pregabalin	16	3.1(2.7)	*6*	19	13	69
vigabatrin	39	2.8(2.0)	*0*	8	23	69
felbamate	33	2.5(2.2)	*0*	12	12	76
methsuximide	15	2.4(2.0)	*0*	*7*	13	80
ketogenic diet	40	1.9(1.4)	*0*	0	13	88
vagus nerve stimulation	37	1.6(1.3)	*0*	0	11	89
ethosuximide	38	1.6(1.1)	*0*	0	11	89
			%	%	%	%

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

2C. Medication recommendations for cryptogenic complex partial seizures

As initial therapy for cryptogenic complex partial seizures, the experts recommended carbamazepine and oxcarbazepine as treatments of choice, with valproate another first-line option, and lamotrigine a high second-line alternatives.
If carbamazepine was used first and was not efficacious or tolerated, then valproate moved up to first line. In the 2005 U.S. pediatric epilepsy survey (Wheless *et al.* 2005), lamotrigine, levetiracetam, and topiramate were rated as first-line options after a failure of carbamazepine, while valproate was a second-line option. These are the same four antiepileptic drugs selected in Europe in this situation, but the order was reversed, likely reflecting a difference in experience with the medications. In both surveys, there was no clear treatment of choice after an initial trial of carbamazepine.
If phenytoin was used first and was not efficacious or tolerated, carbamazepine and oxcarbazepine were the treatments of choice, and valproate was another first-line option to try next. These are essentially the same medications recommended for an untreated child and in the 2005 U.S. pediatric epilepsy survey (Wheless *et al.* 2005), except that valproate was second line.
If oxcarbazepine was used first and was not efficacious or tolerated, none of the options was rated as a treatment of choice, with only valproate rated rated first line as the next option. (In the 2005 U.S. pediatric epilepsy survey [Wheless *et al.* 2005], there was also no treatment of choice after a failure to respond to oxcarbazepine. Again, the same four medications were listed as either first- or second-line options in both surveys, but the order was switched, with valproate receiving first-line ratings in this situation in Europe.) The overall results are consistent with the 2005 European Workshop, which indicated that carbamazepine and oxcarbazepine were first-choice treatments and valproate was a viable alternative (Aldenkamp *et al.* 2006).
After failures of either carbamazepine or oxcarbazepine, the other drug was not picked as a treatment of choice or first-line option for the next treatment, even though the efficacy of each of these drugs has been documented after the failure of the other (Barcs *et al.* 2000, Glauser *et al.* 2000, Schmidt and Elger 2004). One possible explanation for this result is that the molecular similarity of the two agents may have resulted in the belief that, if one failed, the other agent would be more likely to fail as well. However, there are no data in the literature to support this belief.
Based on a recent evidence-based literature review, the American Academy of Neurology and the American Epilepsy Society recommended the use of standard antiepileptic drugs, such as phenobarbital, phenytoin, carbamazepine, or valproic acid, or gabapentin, lamotrigine, topiramate, and oxcarbazepine, among the new antiepileptic drugs, as adjunctive treatment options for refractory pediatric partial-onset epilepsy (French *et al.* 2004b). The same authors note the lack of monotherapy trials in children who have previously failed to respond to an antiepileptic drug.

Clinical situation	Usually appropriate	Sometimes appropriate*
Initial monotherapy	***Carbamazepine*** ***Oxcarbazepine*** Valproate	Lamotrigine
Second monotherapy after initial trial of carbamazepine	Valproate	Lamotrigine Topiramate Oxcarbazepine Levetiracetam
Second monotherapy after initial trial of phenytoin	***Carbamazepine*** ***Oxcarbazepine*** Valproate	Topiramate Lamotrigine Levetiracetam
Second monotherapy after initial trial of oxcarbazepine	Valproate	Lamotrigine Topiramate Levetiracetam

*Equivocal but high second-line ratings.
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

3. Neonatal seizures

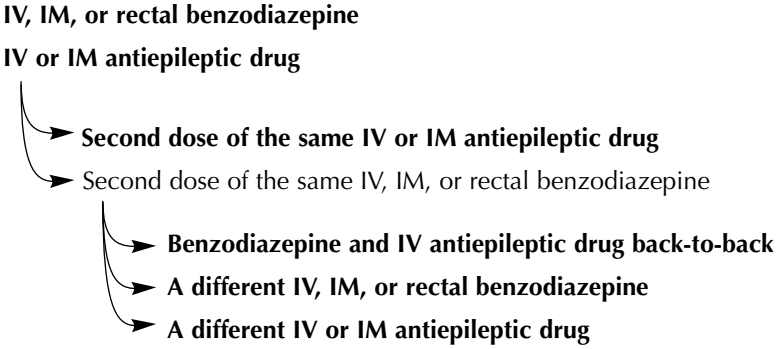
3A. Overall strategies

Question 4. An infant is delivered at age 38-weeks gestation and has onset of seizures that it is suspected are due to hypoxic-ischemic encephalopathy. The infant is now intubated, is having intermittent seizures, and has not yet been treated. Assume the parents are willing to accept all therapies. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

		n for each step					
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**Avg**
IV, IM or rectal benzodiazepine	30	20	1	3	6		1.83
IV or IM AED	39	19	8	8	3	1	1.95
Second dose of same IV, IM, or rectal benzodiazepine	6		3	2	1		2.67
Second dose of same IV or IM AED	21		11	5	3	2	2.81
Benzodiazepine and an IV AED back-to-back	14	1	3	5	4	1	3.07
A different IV, IM, or rectal benzodiazepine	14		7	1	2	4	3.21
A different IV or IM AED	37		6	13	14	4	3.43
Iatrogenic drug coma	22		1	3	4	14	4.41

AED = antiepileptic drug; IM = intramuscular; IV = intravenous.

Comment: while treatment protocols exist for treating status epilepticus in the older child (Wheless and Clarke 2005), no standard protocols exist for the treatment of neonatal status epilepticus. This lack of accepted recommendations and data is reflected in the experts' ratings, which are divided fairly equally among the different options at the various stages of treatment.



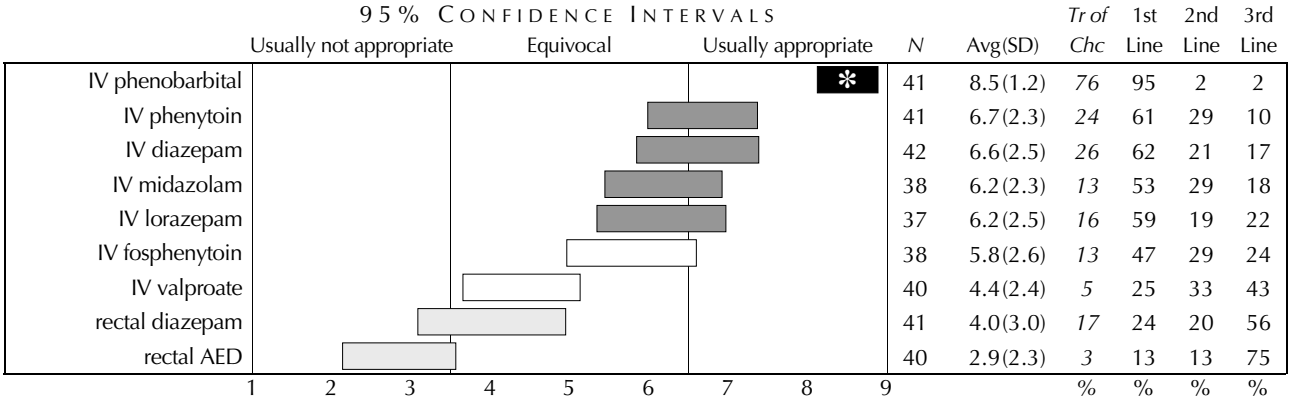
Question 5. The neonatal seizures stopped after the acute event. The infant is now 2 weeks old and is approaching hospital discharge. How long do you continue treatment for neonatal seizures?

Mean ± SD = 13.3 ± 12.2 weeks (range = 2 to 50 weeks, *N* = 33)

Comment: neonatal seizures are a common problem, affecting 1 to 4 infants out of every 1,000 live births (Evans and Levene 1998). However, there are no established guidelines on the best time to stop medications.In the past, neonatal seizures were often treated by continuing medication up to the age of 1 year (Hodson 1985). The suggestion by the experts to continue treatment for only 3 to 4 months reflects the understanding that these are acute symptomatic seizures (Lombroso 1996, Tharp 2002), that prolonged treatment does not prevent the development of subsequent epilepsy (Bergman *et al.* 1983, Gal 1985, Gal *et al.* 1984), or improve the neurologic outcome (Guillet and Kwon 2007), and that continued medication treatment may have deleterious effects on the developing brain (Bittigau *et al.* 2002, 2003, Olney *et al.* 2002).

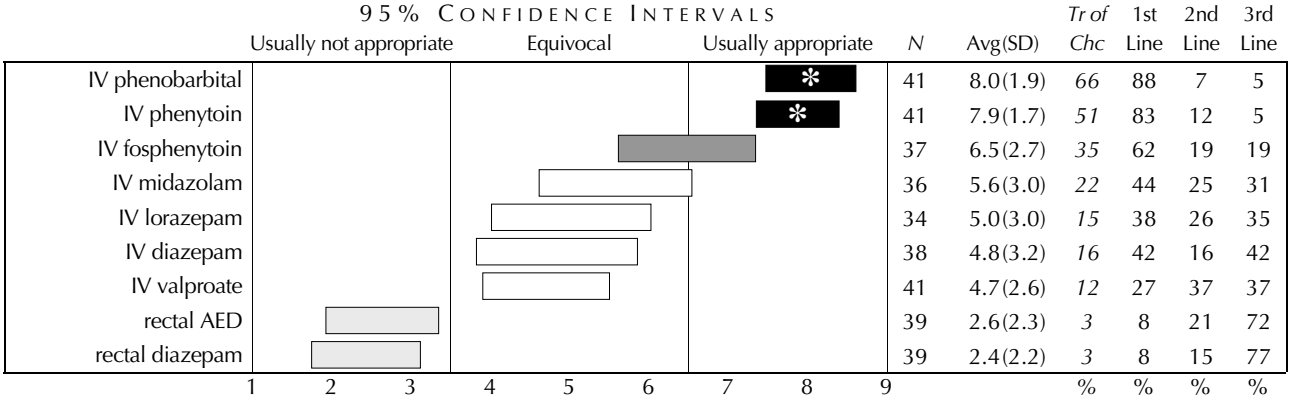
3B. Treatment selection for neonatal seizures: survey results

Question 19. An infant is delivered at age 38-weeks gestation and has onset of seizures that are suspected to be due to ***hypoxic-ischemic encephalopathy***. The infant is now intubated and is having intermittent seizures. No therapy has been tried. Assume the parents are willing to accept all therapies. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated. Please rate the appropriateness of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
IV phenobarbital	41	8.5(1.2)	*76*	95	2	2
IV phenytoin	41	6.7(2.3)	*24*	61	29	10
IV diazepam	42	6.6(2.5)	*26*	62	21	17
IV midazolam	38	6.2(2.3)	*13*	53	29	18
IV lorazepam	37	6.2(2.5)	*16*	59	19	22
IV fosphenytoin	38	5.8(2.6)	*13*	47	29	24
IV valproate	40	4.4(2.4)	*5*	25	33	43
rectal diazepam	41	4.0(3.0)	*17*	24	20	56
rectal AED	40	2.9(2.3)	*3*	13	13	75
			%	%	%	%

Question 20. Assume the first agent used to treat the neonatal seizures was a benzodiazepine, and it has been given to its maximum dose. It has failed to stop the neonatal seizures. Please rate the appropriateness of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
IV phenobarbital	41	8.0(1.9)	*66*	88	7	5
IV phenytoin	41	7.9(1.7)	*51*	83	12	5
IV fosphenytoin	37	6.5(2.7)	*35*	62	19	19
IV midazolam	36	5.6(3.0)	*22*	44	25	31
IV lorazepam	34	5.0(3.0)	*15*	38	26	35
IV diazepam	38	4.8(3.2)	*16*	42	16	42
IV valproate	41	4.7(2.6)	*12*	27	37	37
rectal AED	39	2.6(2.3)	*3*	8	21	72
rectal diazepam	39	2.4(2.2)	*3*	8	15	77
			%	%	%	%

Key

- Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

3C. Medication recommendations for neonatal seizures

Only one randomized, controlled trial in neonatal seizures has been published in full. In that study, Painter *et al.* (1999) found that phenobarbital and phenytoin were equally effective. A subsequent Cochrane review (Evans and Levene 2001) suggested that anticonvulsants could be used to treat seizures in the setting of perinatal asphyxia, but that there was no evidence to recommend their use in routine practice to prevent the morbidity or mortality associated with perinatal asphyxia. A more recent Cochrane review (Booth and Evans 2004) stated that there is little evidence from randomized controlled trials to support the use of any of the currently available anticonvulsants in the neonatal period. Castro Conde *et al.* (2005) suggested midazolam be given to infants who did not respond to phenobarbital or phenytoin. This sequence resulted in improved seizure control and neurodevelopment. Animal studies have suggested that topiramate may effectively treat seizures in rat pups (Koh and Jensen 2001) and improve neurodevelopmental outcome (Zhao *et al.* 2005), but no parenteral formulation of topiramate is available, limiting use of this medication in perinatal hypoxic-ischemic encephalopathy and neonatal seizures.

Clinical situation	Usually appropriate	Sometimes appropriate*
Initial therapy	***IV phenobarbital***	IV phenytoin IV diazepam IV midazolam IV lorazepam
Second monotherapy after initial trial of a benzodiazepine	***IV phenobarbital*** ***IV phenytoin***	IV fosphenytoin

*Equivocal but high second-line ratings; IV = intravenous.

Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

4. Infantile spasms

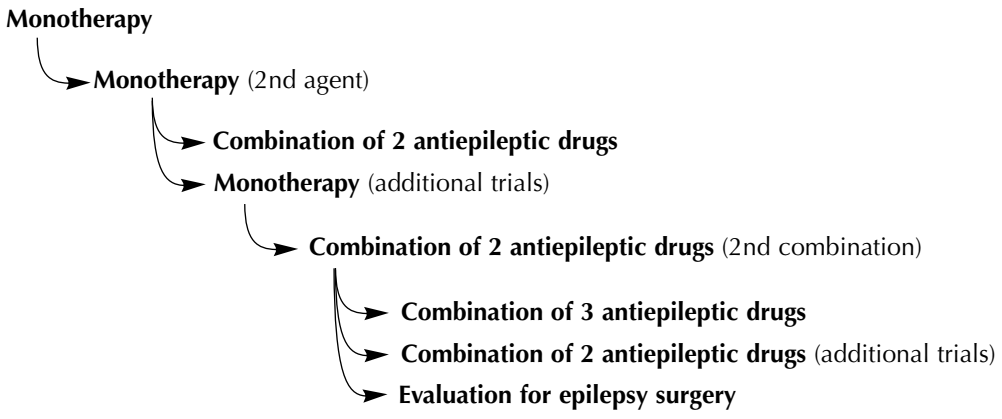
4A. Overall strategies

Question 6. A healthy 6-month-old is diagnosed with ***infantile spasms*** and has not been treated. Assume that the parents are amenable to all possible therapies and will be compliant with the therapy. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

		n for each step							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	40	40							1.00
Monotherapy 2nd agent	26		24	2					2.08
Combination of 2 AEDs	36		16	10	9		1		2.89
Monotherapy (additional trials)	12			10	1	1			3.25
Combination of 2 AEDs (2nd combination)	31			13	7	9	1	1	4.03
Combination of 3 AEDs	22			3	6	3	7	3	5.05
Combination of 2 AEDs (additional trials)	22				7	5	8	2	5.23
Evaluation for epilepsy surgery	26			2	5	6	8	5	5.35
Ketogenic diet (as add-on therapy)	23			1	1	12	3	6	5.52
Combination of 3 AEDs (2nd combination)	14				1	6	3	4	5.71
Ketogenic diet (as monotherapy)	5				1	1	1	2	5.80
Combination of 3 AEDs (additional trials)	4					1	1	2	6.25
Combination of 4 AEDs	6						3	3	6.50
Vagus nerve stimulation (add-on therapy)	3						1	2	6.67
Combination of 4 AEDS (additional trials)	2							2	7.00

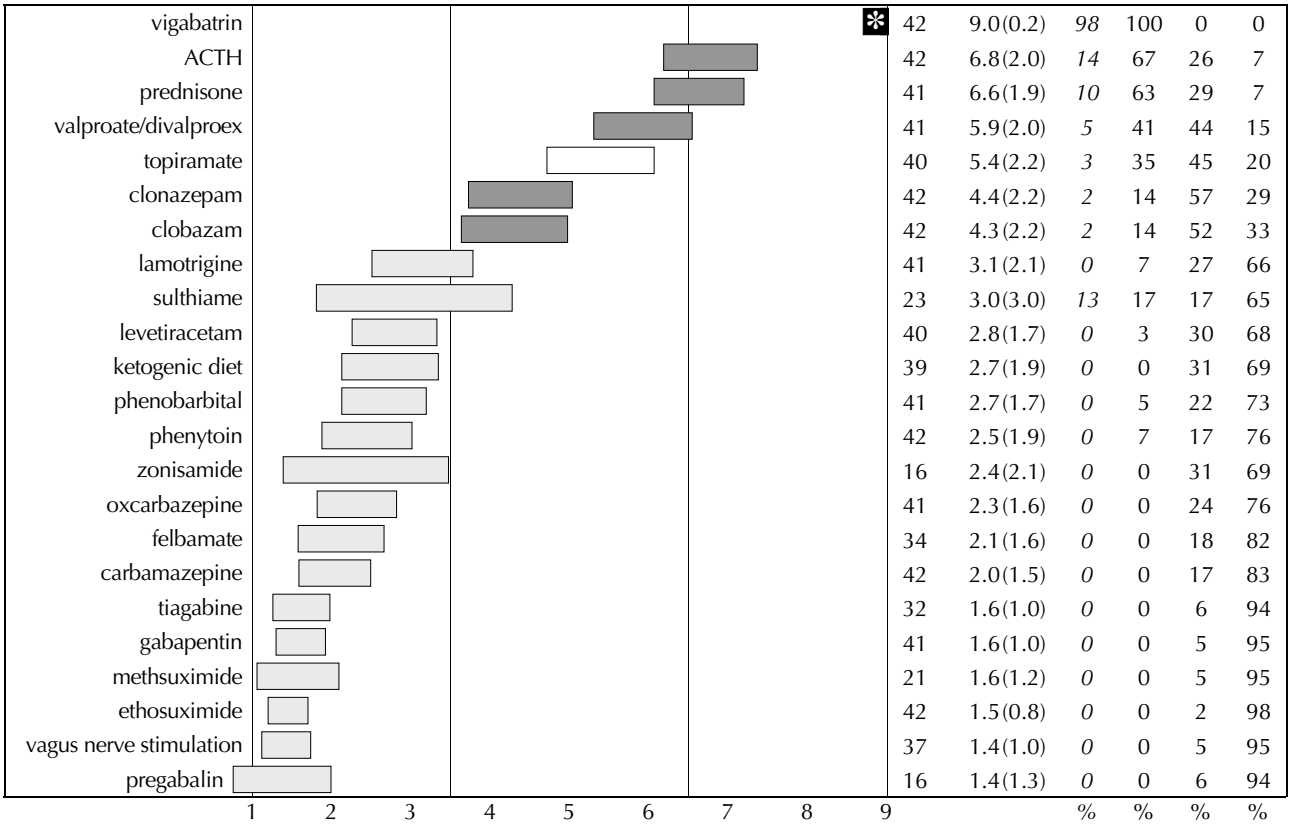
AED = antiepileptic drug.

Comment: all of the experts endorsed a trial of monotherapy at step 1 for a healthy 6-month-old with infantile spasms. At step 2, the experts were split, with 24 (60%) of the responses recommending another trial of monotherapy, while 16 (40%) of the responses endorsed a combination of 2 antiepileptic drugs. At step 3, over half of the responses (56%, 23/41) endorsed use of a combination of 2 antiepileptic drugs, while a quarter (29%, 12/41) endorsed continued trials of monotherapy. The United Kingdom Infantile Spasms Study (UKISS) II will evaluate whether combination therapy is more efficacious than monotherapy at the onset of seizures (Lux *et al.* 2004) (see page S31). At step 4, most of the experts endorsed multiple drug therapy, with 61% (23/38) of the responses favoring use of 2 antiepileptic drugs and 16% (6/38) endorsing a combination of 3 agents, with only 13% of the responses endorsing an evaluation for epilepsy surgery at this stage of treatment. Thus, drug therapy is suggested at the first 4 steps in the treatment of infantile spasms. However, a recent practice parameter from the Child Neurology Society and the American Academy of Neurology concluded that adrenocorticotropic hormone (ACTH) is probably effective and that vigabatrin is possibly effective (Mackay *et al.* 2004), whereas no other medications were considered effective. This observation has prompted others to suggest that children with infantile spasms be treated with the ketogenic diet (Kossoff *et al.* 2002, Wheless 2004) or be evaluated earlier as candidates for epilepsy surgery (Chugani 1995, Chugani *et al.* 1993, Wheless 2004); however, these suggestions were not endorsed by our experts.



4B. Treatment selection for infantile spasms: survey results

Question 21. A healthy 6-month-old is diagnosed with ***infantile spasms secondary to tuberous sclerosis complex*** and is starting therapy for the first time. Assume that you begin with monotherapy. Assume that the parents are amenable to all possible therapies and will be compliant with the therapy. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
vigabatrin ✻	42	9.0(0.2)	*98*	100	0	0
ACTH	42	6.8(2.0)	*14*	67	26	*7*
prednisone	41	6.6(1.9)	*10*	63	29	*7*
valproate/divalproex	41	5.9(2.0)	*5*	41	44	15
topiramate	40	5.4(2.2)	*3*	35	45	20
clonazepam	42	4.4(2.2)	*2*	14	57	29
clobazam	42	4.3(2.2)	*2*	14	52	33
lamotrigine	41	3.1(2.1)	*0*	7	27	66
sulthiame	23	3.0(3.0)	*13*	17	17	65
levetiracetam	40	2.8(1.7)	*0*	3	30	68
ketogenic diet	39	2.7(1.9)	*0*	0	31	69
phenobarbital	41	2.7(1.7)	*0*	5	22	73
phenytoin	42	2.5(1.9)	*0*	7	17	76
zonisamide	16	2.4(2.1)	*0*	0	31	69
oxcarbazepine	41	2.3(1.6)	*0*	0	24	76
felbamate	34	2.1(1.6)	*0*	0	18	82
carbamazepine	42	2.0(1.5)	*0*	0	17	83
tiagabine	32	1.6(1.0)	*0*	0	6	94
gabapentin	41	1.6(1.0)	*0*	0	5	95
methsuximide	21	1.6(1.2)	*0*	0	5	95
ethosuximide	42	1.5(0.8)	*0*	0	2	98
vagus nerve stimulation	37	1.4(1.0)	*0*	0	5	95
pregabalin	16	1.4(1.3)	*0*	0	6	94
			%	%	%	%

Comment: the experts rated vigabatrin treatment of choice for infantile spasms if the etiology is tuberous sclerosis complex, with ACTH and prednisone, followed by valproate, considered sometimes appropriate (high second-line ratings). The recommendation of vigabatrin as treatment of choice is consistent with findings from open-label clinical trials (Curatolo *et al.* 2001, Mackay *et al.* 2002, Thiele 2004). A study in the United Kingdom comparing vigabatrin with prednisone or tetracosactide in infantile spasms excluded infants with tuberous sclerosis complex, since they felt the evidence suggests that vigabatrin is the treatment of choice in these patients (Lux *et al.* 2004). However, a recent Cochrane review (Hancock *et al.* 2003) and the practice parameter of the American Academy of Neurology and the Child Neurology Society (AAN/CNS) (Mackay *et al.* 2004) were less enthusiastic and suggested further trials with vigabatrin.

Key

✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.

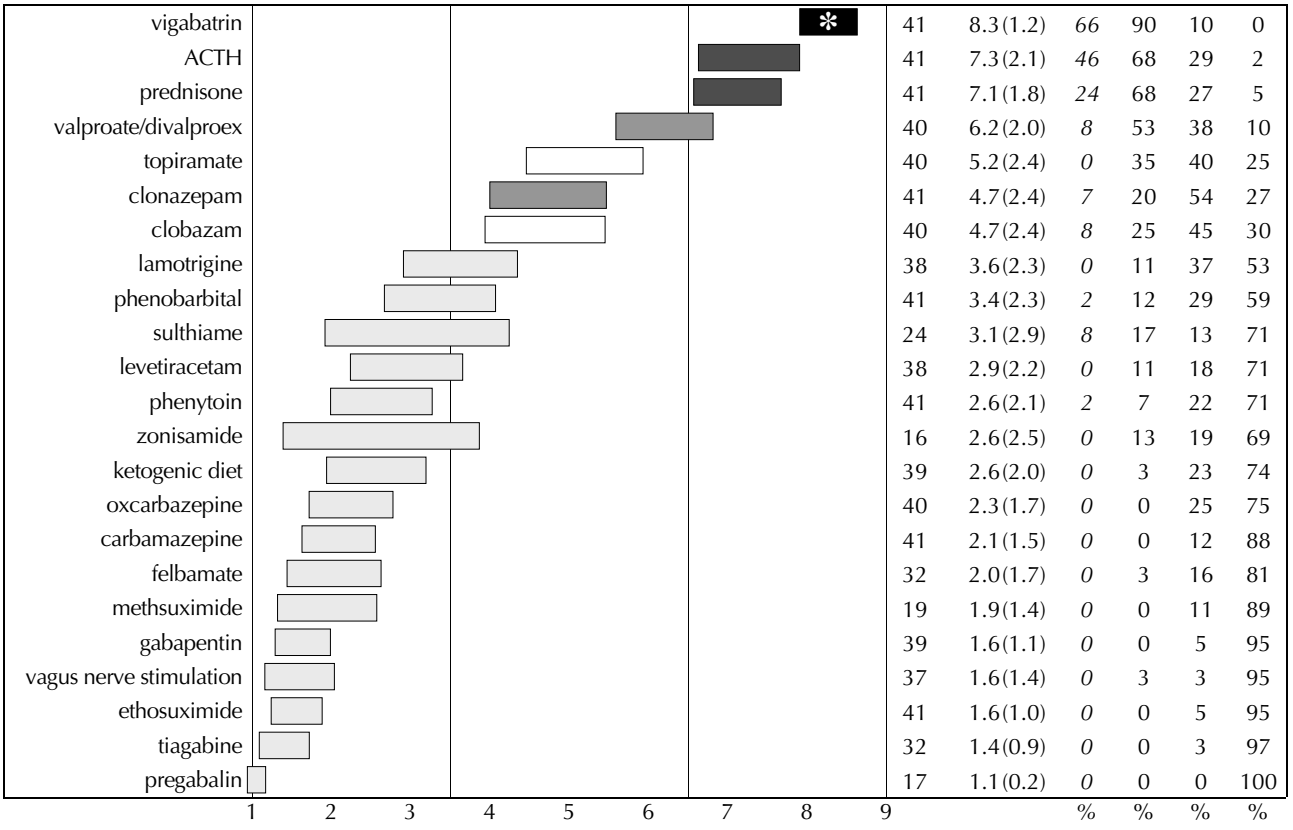
Usually appropriate or first line.

Equivocal or second line.

Usually not appropriate or third line.

No consensus.

Question 22. An otherwise healthy 8-month-old is diagnosed with ***infantile spasms that are symptomatic*** in etiology. The male infant was a product of a 28-week gestational pregnancy and suffered a grade 4 intraventricular hemorrhage. He has a gastrostomy tube in place because of severe gastroesophageal reflux disease and significant dysphagia. He is also cortically blind and has severe developmental delay. Assume the parents are amenable to all possible therapies and will be compliant with therapy. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
vigabatrin	41	8.3(1.2)	*66*	90	10	0
ACTH	41	7.3(2.1)	*46*	68	29	2
prednisone	41	7.1(1.8)	*24*	68	27	5
valproate/divalproex	40	6.2(2.0)	*8*	53	38	10
topiramate	40	5.2(2.4)	*0*	35	40	25
clonazepam	41	4.7(2.4)	*7*	20	54	27
clobazam	40	4.7(2.4)	*8*	25	45	30
lamotrigine	38	3.6(2.3)	*0*	11	37	53
phenobarbital	41	3.4(2.3)	*2*	12	29	59
sulthiame	24	3.1(2.9)	*8*	17	13	71
levetiracetam	38	2.9(2.2)	*0*	11	18	71
phenytoin	41	2.6(2.1)	*2*	7	22	71
zonisamide	16	2.6(2.5)	*0*	13	19	69
ketogenic diet	39	2.6(2.0)	*0*	3	23	74
oxcarbazepine	40	2.3(1.7)	*0*	0	25	75
carbamazepine	41	2.1(1.5)	*0*	0	12	88
felbamate	32	2.0(1.7)	*0*	3	16	81
methsuximide	19	1.9(1.4)	*0*	0	11	89
gabapentin	39	1.6(1.1)	*0*	0	5	95
vagus nerve stimulation	37	1.6(1.4)	*0*	3	3	95
ethosuximide	41	1.6(1.0)	*0*	0	5	95
tiagabine	32	1.4(0.9)	*0*	0	3	97
pregabalin	17	1.1(0.2)	*0*	0	0	100
			%	%	%	%

Comment: the experts rated vigabatrin as treatment of choice for infantile spasms that are symptomatic in etiology, with ACTH and prednisone other first-line options. The experts considered valproate sometimes appropriate (high second-line ratings). The experts' endorsement of vigabatrin as treatment for infantile spasms is not consistent with the American Academy of Neurology and the Child Neurology Society (AAN/CNS) 2004 practice parameter (Mackay *et al.* 2004). However, this publication did not specifically address the treatment of children with symptomatic infantile spasms who typically have a poorer response to treatment (Fejerman *et al.* 2000). The UKISS also found that hormonal therapy was significantly more likely than vigabatrin to cause cessation of spasms and resolution of hypsarrhythmia by day 14 of treatment (Lux *et al.* 2004). However, at age 14 months, there was no difference in spasm control or neurodevelopment, except for the group of infants with no identified underlying etiology (Lux *et al.* 2005). Consideration of this long-term outcome, the possible lethal side effects of hormonal therapy, and the ease of initiating treatment with vigabatrin may explain why the experts chose vigabatrin as the treatment of choice in symptomatic infantile spasms. Topiramate (Glauser *et al.* 1998, Hosain *et al.* 2006, Kwon *et al.* 2006, Thijs *et al.* 2001, Zou *et al.* 2006) and zonisamide (Suzuki 2001, Yanagaki *et al.* 2005) have been used in this specific population in open-label studies with some efficacy, but no controlled studies have been done with these agents, which may account for their lower ratings here.

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

4C. Medication recommendations for infantile spasms

The experts' treatments of choice recommendation for infantile spasms (West syndrome) was vigabatrin no matter what the etiology of the spasms. Other first-line options for spasms that are symptomatic in etiology were ACTH and prednisone. The 2003 National Institute for Clinical Excellence (NICE) Guidelines (2004), the 2005 Scottish Intercollegiate Guidelines Network (SIGN) Guidelines (2005), and the 2005 U.S. Pediatric Epilepsy survey (Wheless *et al.* 2005) all support the use of vigabatrin as first-line therapy for infantile spasms associated with tuberous sclerosis complex. However, only the NICE Guidelines support vigabatrin as the drug of choice in symptomatic infantile spasms. The U.S. survey and the SIGN Guidelines suggest ACTH as the first-line therapy, a finding recently supported by the UKISS (Lux *et al.* 2004), which showed greater efficacy for hormonal therapy compared with vigabatrin after 2 weeks of treatment. However, these same researchers found no difference in control of symptomatic infantile spasms or improved developmental outcome in these infants, whether vigabatrin or hormonal therapy was used (Lux *et al.* 2005). This finding may be the reason the European experts in our survey selected vigabatrin as drug of choice in symptomatic infantile spasms.
Symptomatic infantile spasms are difficult to treat, and the lack of an apparent long-term difference in efficacy between vigabatrin and hormonal therapy has led to the investigation of other options. Preliminary data (Zafeiriou *et al.* 1996) suggested that these children may benefit from combination therapy with ACTH and vigabatrin at the time of diagnosis. This strategy is being studied in the ongoing UKISS II trial, which is comparing hormonal therapy with combination treatment involving vigabatrin plus hormonal therapy. When this trial is completed, we will have better information available on how to treat children with this challenging epilepsy syndrome.

Clinical situation	Usually appropriate	Sometimes appropriate*
Infantile spasms secondary to tuberous sclerosis complex	***Vigabatrin***	ACTH Prednisone Valproate
Infantile spasms that are symptomatic in etiology	***Vigabatrin*** ACTH Prednisone	Valproate

*Equivocal but high second-line ratings.
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

5. Lennox-Gastaut syndrome

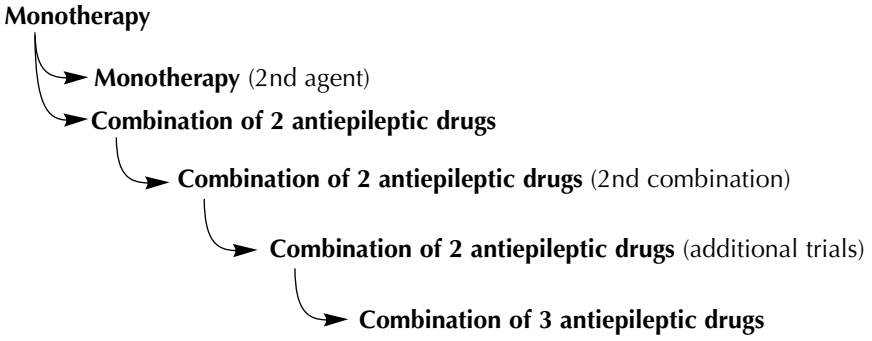
5A. Overall strategy

Question 7. A healthy 4-year-old female is diagnosed with ***Lennox-Gastaut syndrome*** consisting of frequent astatic seizures and only occasional generalized tonic-clonic and atypical absence seizures and has not been treated yet. Assume the family is willing to accept all treatments and will be compliant. Assume that each treatment is increased to the limit of clinical tolerability before new treatment is initiated.

		***n* for each step**							
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Avg**
Monotherapy	38	38							1.00
Monotherapy 2nd agent	17		16				1		2.24
Combination of 2 AEDs	38	2	24	11	1				2.29
Monotherapy (additional trials)	5			5					3.00
Combination of 2 AEDs (2nd combination)	36		1	24	8	2	1		3.39
Combination of 2 AEDs (additional trials)	26			1	16	5	4		4.46
Ketogenic diet (as monotherapy)	6				3	1	2		4.83
Combination of 3 AEDs	32		1		10	17		4	4.84
Ketogenic diet (as add-on therapy)	25			1	3	4	10	7	5.76
Combination of 4 AEDs	9					4	3	2	5.78
Combination of 3 AEDs (2nd combination)	19					5	10	4	5.95
Evaluation for epilepsy surgery	19				2	5	3	9	6.00
Vagus nerve stimulation (add-on therapy)	19				1	3	3	12	6.37
Combination of 3 AEDs (additional trials)	9					1	3	5	6.44
Combination of 4 AEDS (additional trials)	6						3	3	6.50

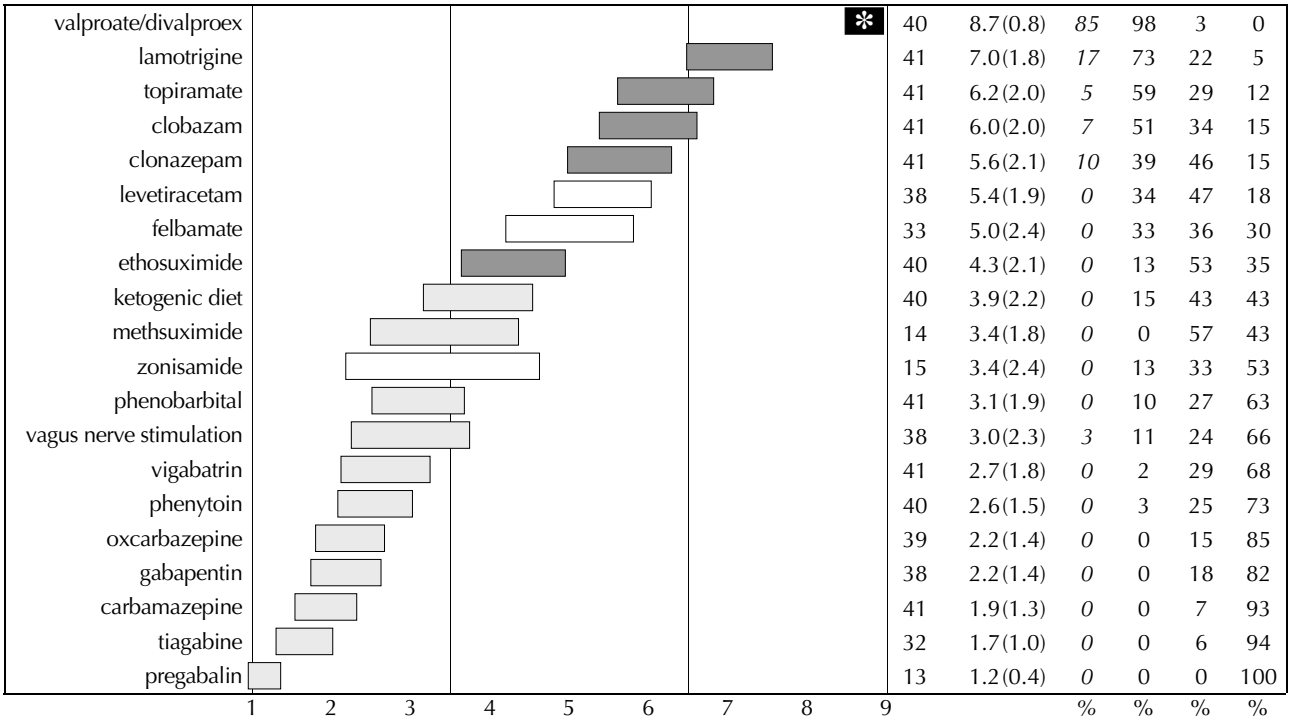
AED = antiepileptic drug.

Comment: at step 1, nearly all of the experts supported a trial of monotherapy for a child with Lennox-Gastaut syndrome. If the initial monotherapy is not successful, 57% (24/42) of the responses endorsed a combination of 2 antiepileptic drugs, while 38% (16/42) would try a different monotherapy at step 2. At step 3, 86% (36/42) of the responses favored a combination of 2 antiepileptic drugs. At step 4, the experts endorsed a variety of strategies; however, over half of the responses (25/44, 57%) supported trying additional combinations of 2 antiepileptic drugs, while 23% (10/44) would move on to a combination of 3 drugs. The experts did not recommend surgical treatment (callosotomy) or vagus nerve stimulation for a child with Lennox-Gastaut syndrome and frequent astatic seizures except as a last choice. However, vagus nerve stimulation (Frost *et al.* 2001, Hosain *et al.* 2000, Karceski 2001) and callosotomy (Trevathan 2002, Wheless 2004) have both shown efficacy in the treatment of astatic seizures in open-label studies. Controlled trials may be necessary to improve the recommendations for the use of these procedures in treating this devastating seizure type.



5B. Treatment selection for Lennox-Gastaut syndrome: survey results

Question 23. A healthy 6-year-old child has ***Lennox-Gastaut syndrome*** with infrequent generalized tonic-clonic and atypical absence seizures but multiple daily astatic seizures. The patient is being treated for the first time. Assume that you begin with monotherapy. Assume the parents are amenable to all therapies and that they will be compliant with therapy. Please keep in mind the dominant seizure type the patient is experiencing (within the diagnosis). Rate the appropriateness of each of the following treatments.

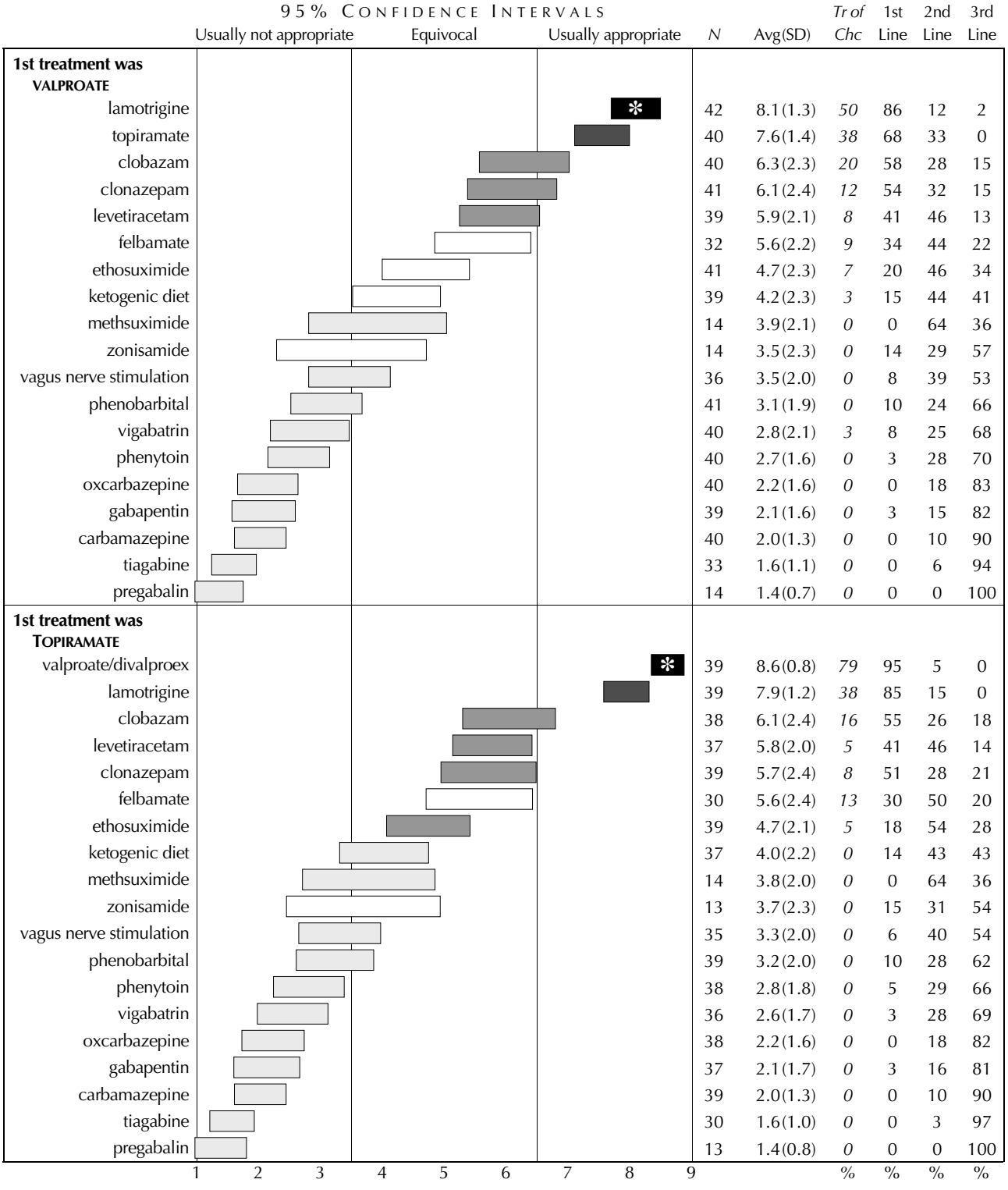


	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
valproate/divalproex	40	8.7(0.8)	*85*	98	3	0
lamotrigine	41	7.0(1.8)	*17*	73	22	5
topiramate	41	6.2(2.0)	*5*	59	29	12
clobazam	41	6.0(2.0)	*7*	51	34	15
clonazepam	41	5.6(2.1)	*10*	39	46	15
levetiracetam	38	5.4(1.9)	*0*	34	47	18
felbamate	33	5.0(2.4)	*0*	33	36	30
ethosuximide	40	4.3(2.1)	*0*	13	53	35
ketogenic diet	40	3.9(2.2)	*0*	15	43	43
methsuximide	14	3.4(1.8)	*0*	0	57	43
zonisamide	15	3.4(2.4)	*0*	13	33	53
phenobarbital	41	3.1(1.9)	*0*	10	27	63
vagus nerve stimulation	38	3.0(2.3)	*3*	11	24	66
vigabatrin	41	2.7(1.8)	*0*	2	29	68
phenytoin	40	2.6(1.5)	*0*	3	25	73
oxcarbazepine	39	2.2(1.4)	*0*	0	15	85
gabapentin	38	2.2(1.4)	*0*	0	18	82
carbamazepine	41	1.9(1.3)	*0*	0	7	93
tiagabine	32	1.7(1.0)	*0*	0	6	94
pregabalin	13	1.2(0.4)	*0*	0	0	100
			%	%	%	%

Key

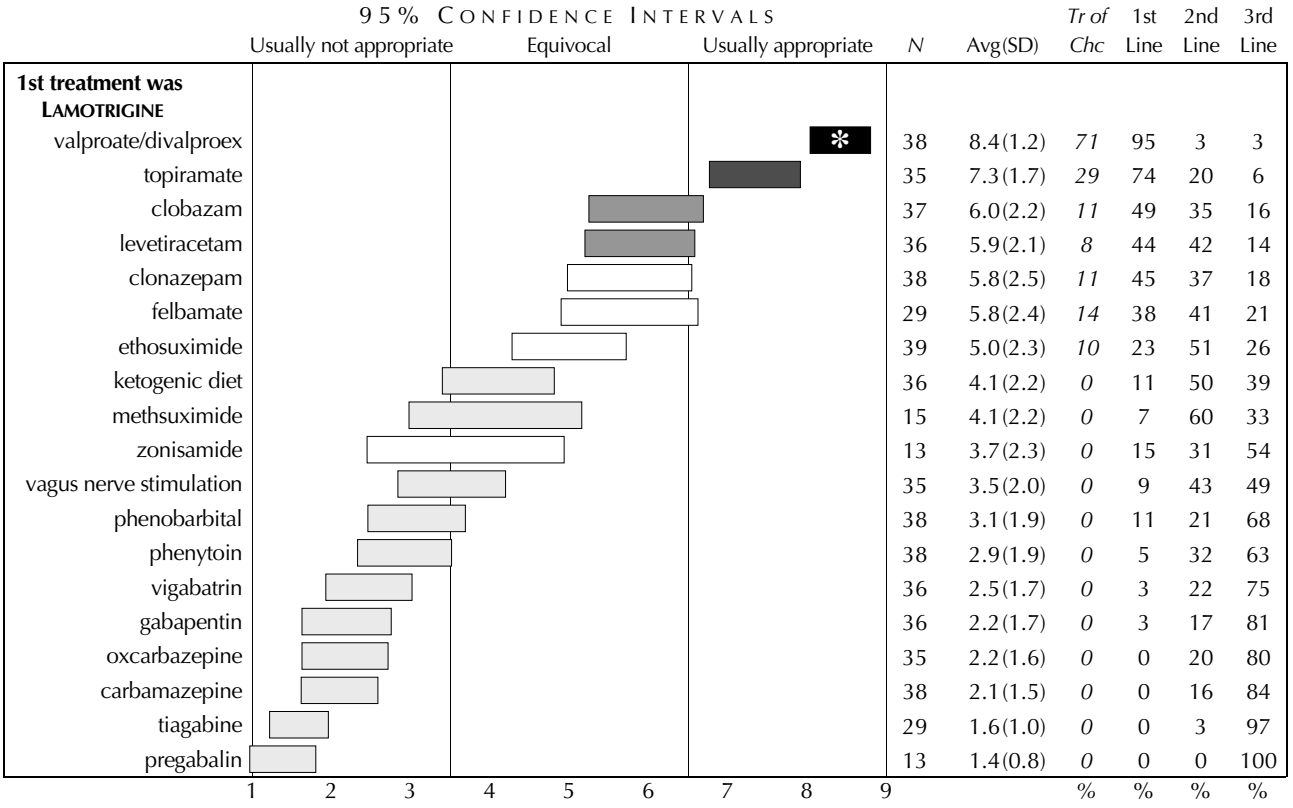
- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

Question 24. Assume that the first treatment you select is valproate, lamotrigine, or topiramate. The child has no reduction in seizures, a limited response, or the medication is poorly tolerated. Assume you choose a second monotherapy trial. As in question 23, the child has Lennox-Gastaut syndrome with infrequent generalized tonic-clonic and atypical absence seizures but multiple daily astatic seizures. Rate the appropriateness of each of the following treatments as second monotherapy.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
1st treatment was VALPROATE						
lamotrigine	42	8.1(1.3)	*50*	86	12	2
topiramate	40	7.6(1.4)	*38*	68	33	0
clobazam	40	6.3(2.3)	*20*	58	28	15
clonazepam	41	6.1(2.4)	*12*	54	32	15
levetiracetam	39	5.9(2.1)	*8*	41	46	13
felbamate	32	5.6(2.2)	*9*	34	44	22
ethosuximide	41	4.7(2.3)	*7*	20	46	34
ketogenic diet	39	4.2(2.3)	*3*	15	44	41
methsuximide	14	3.9(2.1)	*0*	0	64	36
zonisamide	14	3.5(2.3)	*0*	14	29	57
vagus nerve stimulation	36	3.5(2.0)	*0*	8	39	53
phenobarbital	41	3.1(1.9)	*0*	10	24	66
vigabatrin	40	2.8(2.1)	*3*	8	25	68
phenytoin	40	2.7(1.6)	*0*	3	28	70
oxcarbazepine	40	2.2(1.6)	*0*	0	18	83
gabapentin	39	2.1(1.6)	*0*	3	15	82
carbamazepine	40	2.0(1.3)	*0*	0	10	90
tiagabine	33	1.6(1.1)	*0*	0	6	94
pregabalin	14	1.4(0.7)	*0*	0	0	100
1st treatment was TOPIRAMATE						
valproate/divalproex	39	8.6(0.8)	*79*	95	5	0
lamotrigine	39	7.9(1.2)	*38*	85	15	0
clobazam	38	6.1(2.4)	*16*	55	26	18
levetiracetam	37	5.8(2.0)	*5*	41	46	14
clonazepam	39	5.7(2.4)	*8*	51	28	21
felbamate	30	5.6(2.4)	*13*	30	50	20
ethosuximide	39	4.7(2.1)	*5*	18	54	28
ketogenic diet	37	4.0(2.2)	*0*	14	43	43
methsuximide	14	3.8(2.0)	*0*	0	64	36
zonisamide	13	3.7(2.3)	*0*	15	31	54
vagus nerve stimulation	35	3.3(2.0)	*0*	6	40	54
phenobarbital	39	3.2(2.0)	*0*	10	28	62
phenytoin	38	2.8(1.8)	*0*	5	29	66
vigabatrin	36	2.6(1.7)	*0*	3	28	69
oxcarbazepine	38	2.2(1.6)	*0*	0	18	82
gabapentin	37	2.1(1.7)	*0*	3	16	81
carbamazepine	39	2.0(1.3)	*0*	0	10	90
tiagabine	30	1.6(1.0)	*0*	0	3	97
pregabalin	13	1.4(0.8)	*0*	0	0	100
			%	%	%	%

Question 24. *Continued*



1st treatment was LAMOTRIGINE	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
valproate/divalproex	38	8.4(1.2)	*71*	95	3	3
topiramate	35	7.3(1.7)	*29*	74	20	6
clobazam	37	6.0(2.2)	*11*	49	35	16
levetiracetam	36	5.9(2.1)	*8*	44	42	14
clonazepam	38	5.8(2.5)	*11*	45	37	18
felbamate	29	5.8(2.4)	*14*	38	41	21
ethosuximide	39	5.0(2.3)	*10*	23	51	26
ketogenic diet	36	4.1(2.2)	*0*	11	50	39
methsuximide	15	4.1(2.2)	*0*	7	60	33
zonisamide	13	3.7(2.3)	*0*	15	31	54
vagus nerve stimulation	35	3.5(2.0)	*0*	9	43	49
phenobarbital	38	3.1(1.9)	*0*	11	21	68
phenytoin	38	2.9(1.9)	*0*	5	32	63
vigabatrin	36	2.5(1.7)	*0*	3	22	75
gabapentin	36	2.2(1.7)	*0*	3	17	81
oxcarbazepine	35	2.2(1.6)	*0*	0	20	80
carbamazepine	38	2.1(1.5)	*0*	0	16	84
tiagabine	29	1.6(1.0)	*0*	0	3	97
pregabalin	13	1.4(0.8)	*0*	0	0	100
			%	%	%	%

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

5C. Medication recommendations for Lennox-Gastaut syndrome

Since the first report of the use of valproate (Covanis *et al.* 1982) to treat Lennox-Gastaut syndrome, this agent has been considered the treatment of choice as initial therapy (Karceski 2001, Schmidt and Bourgeois 2000), although no controlled trials have validated this opinion. Our experts concurred and considered valproate the treatment of choice, with lamotrigine, topiramate, and clobazam sometimes appropriate (high-second line options) as initial therapy. Ethosuximide was also a second-line option, probably reflecting the fact that this agent is sometimes used in combination with valproate (Genton and Bureau 2006, Ohtsuka *et al.* 2006, Schmidt and Bourgeois 2000). The U.S. experts rated ethosuximide as usually not appropriate (Wheless *et al.* 2005). Controlled trials with felbamate (Dodson 1993, Felbamate Study Group 1993), lamotrigine (Motte *et al.* 1997), and topiramate (Sachdeo *et al.* 1999) have documented the efficacy of these three medications, with resultant U.S. Food and Drug Administration approval and labeled use in Lennox-Gastaut syndrome (Thomson PDR 2007). A recent Cochrane review concurred that these three agents have efficacy as add-on therapy in Lennox-Gastaut syndrome (Hancock and Cross 2003). However, concerns over potential hepatotoxicity and aplastic anemia (Pellock 1999a) have limited the use of felbamate, even though an American Academy of Neurology practice advisory (French *et al.* 1999) stated that the medication may still offer benefit to patients over 4 years of age with Lennox-Gastaut syndrome who are unresponsive to primary antiepileptic drugs. Concern about these potentially fatal side effects may explain the lower ratings and lack of consensus for felbamate .

Based on a recent evidence-based literature review, the American Academy of Neurology and the American Epilepsy Society recommend the use of topiramate and lamotrigine among the new antiepileptic drugs to treat drop attacks (astatic seizures) associated with Lennox-Gastaut Syndrome (French *et al.* 2004b). Clobazam has demonstrated efficacy in the management of Lennox-Gastaut syndrome in European studies (Ng and Collins 2007) and a recent retrospective study (Silva *et al.* 2006). A Phase 2 study evaluating the efficacy of clobazam as adjunctive therapy in Lennox-Gastaut syndrome has just been completed in the United States.

For children who were unresponsive to an initial trial of valproate, lamotrigine was the treatment of choice as the next option, with topiramate another first-line option. The experts considered clobazam, clonazepam, and levetiracetam sometimes appropriate (high second line) for such patients (De Los Reyes *et al.* 2004, Ng and Collins 2007, Silva *et al.* 2006, Sankar *et al.* 2005). For children who received topiramate as initial therapy and did not respond, valproate is the treatment of choice and lamotrigine another first-line choice for the next option. For children who received lamotrigine as initial therapy and did not respond, valproate is treatment of choice and topiramate another first-line choice for the next option.

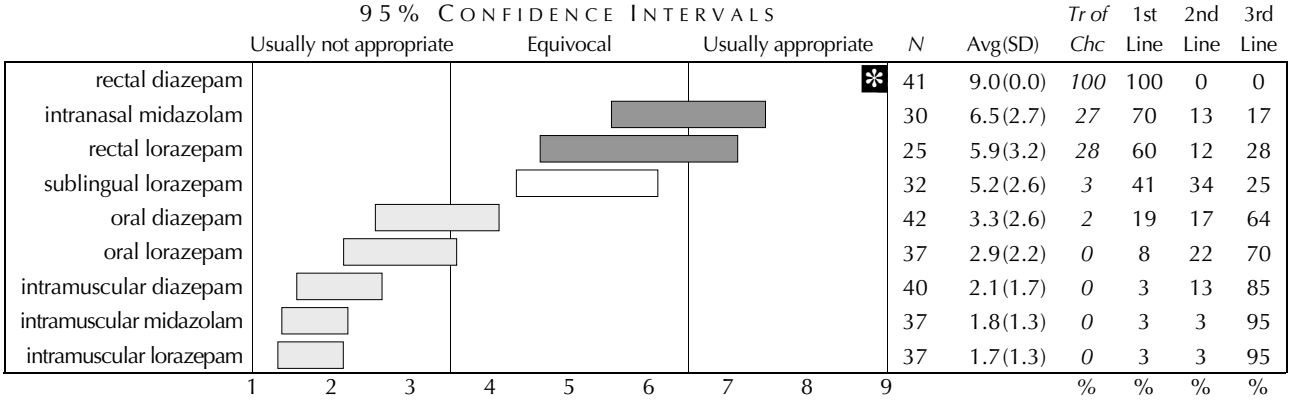
Clinical situation	**Usually appropriate**	**Sometimes appropriate***
Initial monotherapy	***Valproate***	Lamotrigine Topiramate Clobazam
Second monotherapy after an initial trial of valproate	***Lamotrigine*** Topiramate	Clobazam Clonazepam Levetiracetam
Second monotherapy after an initial trial of topiramate	***Valproate*** Lamotrigine	Clobazam
Second monotherapy after an initial trial of lamotrigine	***Valproate*** Topiramate	Clobazam Levetiracetam

*Equivocal but high second-line ratings.

Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

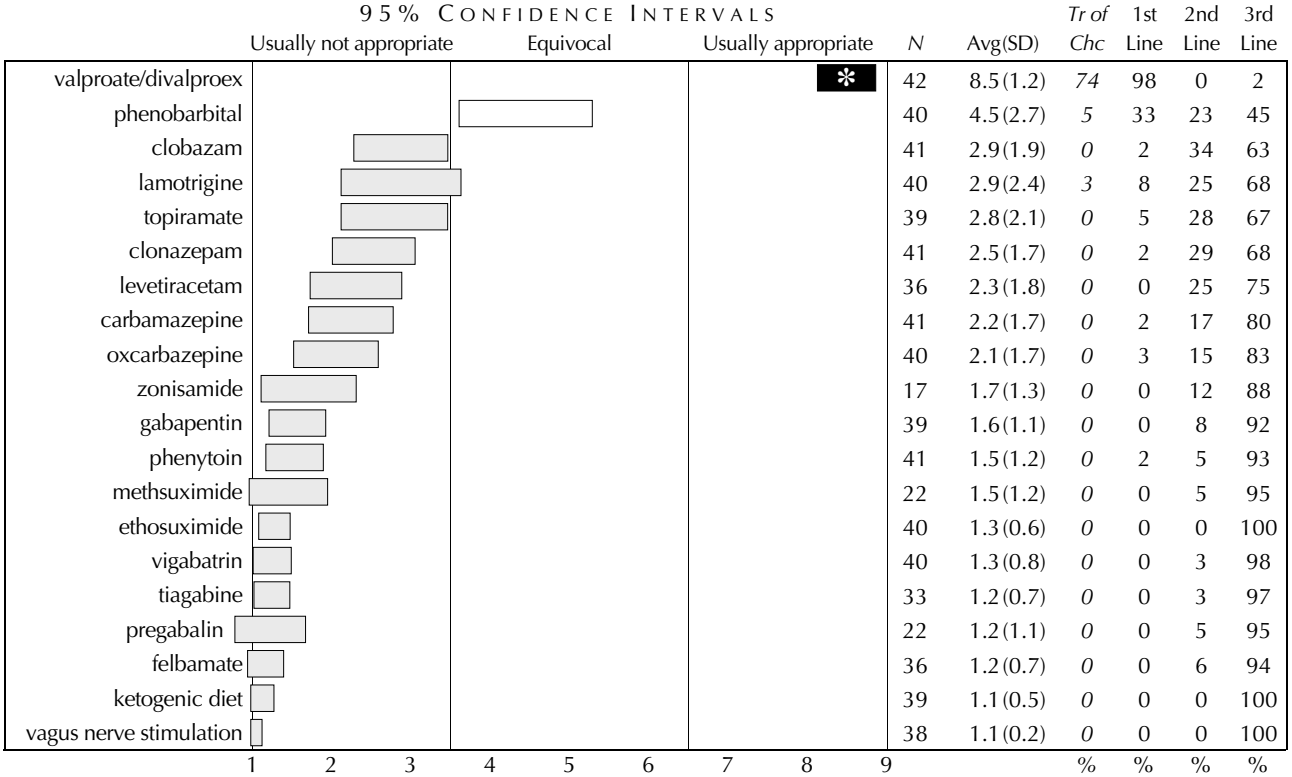
6. Febrile seizures

Question 25. A healthy 12-month-old infant has had his ***first generalized tonic-clonic febrile seizure***. The parents are anxious and ask about medicine to be used acutely at the time of recurrent, prolonged febrile seizures or a cluster of febrile seizures. Assume the parents are amenable to all possible therapies and will be compliant with the therapy. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
rectal diazepam	41	9.0(0.0)	*100*	100	0	0
intranasal midazolam	30	6.5(2.7)	*27*	70	13	17
rectal lorazepam	25	5.9(3.2)	*28*	60	12	28
sublingual lorazepam	32	5.2(2.6)	*3*	41	34	25
oral diazepam	42	3.3(2.6)	*2*	19	17	64
oral lorazepam	37	2.9(2.2)	*0*	8	22	70
intramuscular diazepam	40	2.1(1.7)	*0*	3	13	85
intramuscular midazolam	37	1.8(1.3)	*0*	3	3	95
intramuscular lorazepam	37	1.7(1.3)	*0*	3	3	95
			%	%	%	%

Question 26. A healthy 12-month-old infant is diagnosed with ***recurrent febrile generalized tonic-clonic seizures***. The infant has had five generalized tonic-clonic seizures, all associated with fever since age 6 months. The parents are desirous of pursuing preventive therapy for his febrile seizures. The child is being treated for the first time. Assume you begin with monotherapy and the parents are amenable to all therapies and will be compliant. Rate the appropriateness of each of the following treatments.



	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
valproate/divalproex	42	8.5(1.2)	*74*	98	0	2
phenobarbital	40	4.5(2.7)	*5*	33	23	45
clobazam	41	2.9(1.9)	*0*	2	34	63
lamotrigine	40	2.9(2.4)	*3*	8	25	68
topiramate	39	2.8(2.1)	*0*	5	28	67
clonazepam	41	2.5(1.7)	*0*	2	29	68
levetiracetam	36	2.3(1.8)	*0*	0	25	75
carbamazepine	41	2.2(1.7)	*0*	2	17	80
oxcarbazepine	40	2.1(1.7)	*0*	3	15	83
zonisamide	17	1.7(1.3)	*0*	0	12	88
gabapentin	39	1.6(1.1)	*0*	0	8	92
phenytoin	41	1.5(1.2)	*0*	2	5	93
methsuximide	22	1.5(1.2)	*0*	0	5	95
ethosuximide	40	1.3(0.6)	*0*	0	0	100
vigabatrin	40	1.3(0.8)	*0*	0	3	98
tiagabine	33	1.2(0.7)	*0*	0	3	97
pregabalin	22	1.2(1.1)	*0*	0	5	95
felbamate	36	1.2(0.7)	*0*	0	6	94
ketogenic diet	39	1.1(0.5)	*0*	0	0	100
vagus nerve stimulation	38	1.1(0.2)	*0*	0	0	100
			%	%	%	%

6B. Medication recommendations for febrile seizures

Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or a cluster of febrile seizures, while intranasal midazolam and rectal lorazepam received equivocal (sometimes appropriate) ratings. In the United States, rectal diazepam does not have formal approval from the U.S. Food and Drug Administration as a treatment for febrile seizures or prolonged seizures in children below the age of 2 years (Thomson PDR 2007). However, the use of rectal diazepam in prolonged febrile seizures is supported based on its efficacy as a treatment for acute seizures (Shinnar and Glauser 2002). Valproate was rated treatment of choice as preventive therapy for febrile seizures. Phenobarbital and valproic acid are the only two medications that have shown efficacy in preventing febrile seizures (Baumann 1999). However, concerns over the risks and potential side effects of these medications have resulted in the American Academy of Pediatrics Practice Parameter recommending no therapy for the child who has had one or more simple febrile seizures (American Academy of Pediatrics 1999). This is consistent with the recommendations of the 2005 Scottish Intercollegiate Guidelines Network (2005), even though several new antiepileptic drugs have been introduced since the American Academy of Pediatrics Practice Parameter was published.

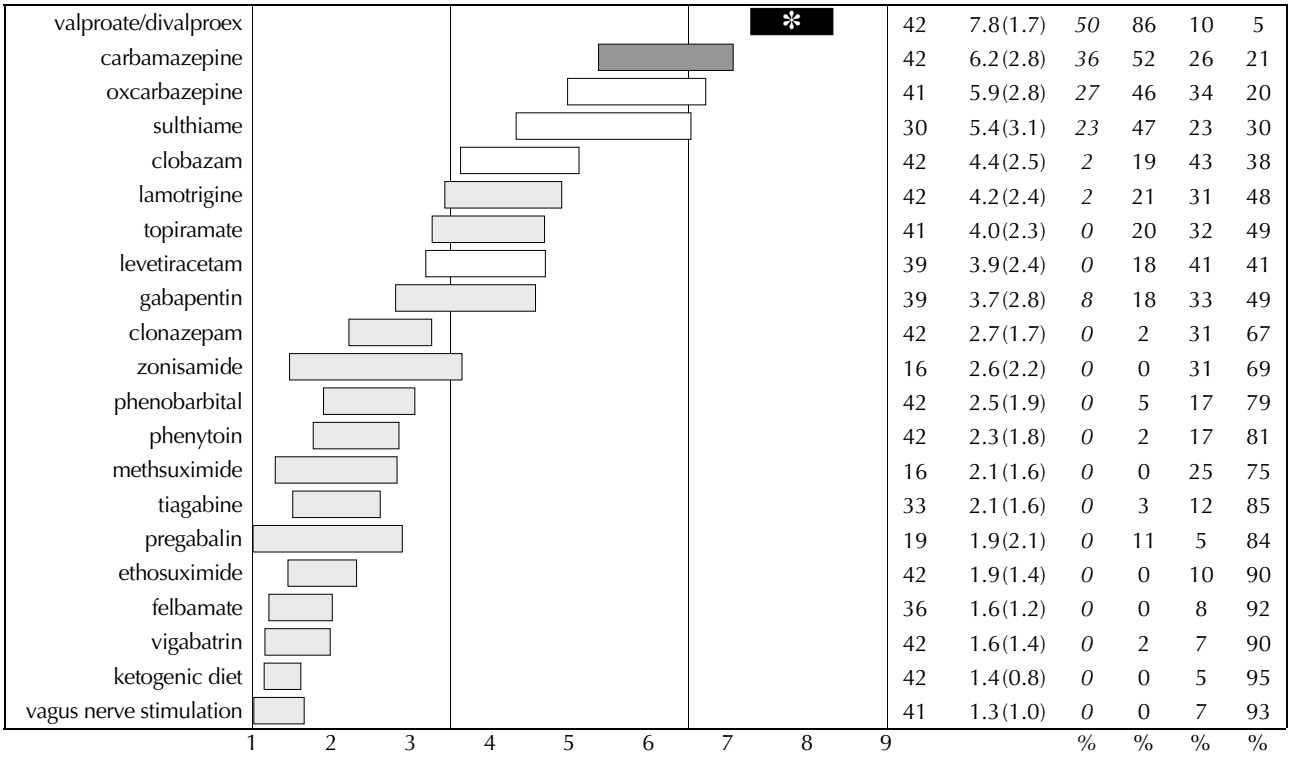
Clinical situation	Usually appropriate	Sometimes appropriate*
Medication to be used acutely at the time of recurrent, prolonged febrile seizures or a cluster of febrile seizures in a healthy 12-month old	***Rectal diazepam***	Intranasal midazolam Rectal lorazepam
Preventive therapy for febrile seizures	***Valproate***	—

*Equivocal but high second-line ratings.
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

7. Benign childhood epilepsy with centro-temporal spikes

7A. Survey results

Question 29. A healthy 8-year-old is diagnosed with ***benign childhood epilepsy with centro-temporal spikes*** (benign rolandic epilepsy of childhood). The child has had enough seizures that the parents and you wish to start therapy for the first time. Assume you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Please keep in mind the epilepsy syndrome the child has and rate the appropriateness of each of the following treatments.



	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
valproate/divalproex	42	7.8(1.7)	*50*	86	10	5
carbamazepine	42	6.2(2.8)	*36*	52	26	21
oxcarbazepine	41	5.9(2.8)	*27*	46	34	20
sulthiame	30	5.4(3.1)	*23*	47	23	30
clobazam	42	4.4(2.5)	*2*	19	43	38
lamotrigine	42	4.2(2.4)	*2*	21	31	48
topiramate	41	4.0(2.3)	*0*	20	32	49
levetiracetam	39	3.9(2.4)	*0*	18	41	41
gabapentin	39	3.7(2.8)	*8*	18	33	49
clonazepam	42	2.7(1.7)	*0*	2	31	67
zonisamide	16	2.6(2.2)	*0*	0	31	69
phenobarbital	42	2.5(1.9)	*0*	5	17	79
phenytoin	42	2.3(1.8)	*0*	2	17	81
methsuximide	16	2.1(1.6)	*0*	0	25	75
tiagabine	33	2.1(1.6)	*0*	3	12	85
pregabalin	19	1.9(2.1)	*0*	11	5	84
ethosuximide	42	1.9(1.4)	*0*	0	10	90
felbamate	36	1.6(1.2)	*0*	0	8	92
vigabatrin	42	1.6(1.4)	*0*	2	7	90
ketogenic diet	42	1.4(0.8)	*0*	0	5	95
vagus nerve stimulation	41	1.3(1.0)	*0*	0	7	93
			%	%	%	%

7B. Medication recommendations for benign childhood epilepsy with centro-temporal spikes

Valproate was considered treatment of choice, while carbamazepine was rated as sometimes appropriate. There was no consensus on oxcarbazepine or sulthiame, although they were rated first line by over 40% of the experts. Sulthiame is considered a first-line drug in those countries in which it is available (German-speaking countries, Japan, and Israel) (Aldenkamp *et al.* 2006). Compare these recommendations to those for cryptogenic complex partial seizures (page S21), where carbamazepine and oxcarbazepine were treatments of choice and valproate was another first-line option. Note that gabapentin received third-line ratings, despite its safety profile and documented efficacy in benign childhood epilepsy with centro-temporal spikes (Morris 1999). Gabapentin and sulthiame (Bast *et al.* 2003, Rating *et al.* 2000) are the only two medications that have been evaluated for the treatment of benign childhood epilepsy with centro-temporal spikes in multi-center, double-blind, randomized trials and both have documented efficacy. Carbamazepine and oxcarbazepine, while often used to treat benign childhood epilepsy with centro-temporal spikes, may be associated in rare cases with seizure aggravation in benign childhood epilepsy with centro-temporal spikes (Corda *et al.* 2001, Grosso *et al.* 2006, Rating 2000), which is something clinicians should be aware of when using this agent.

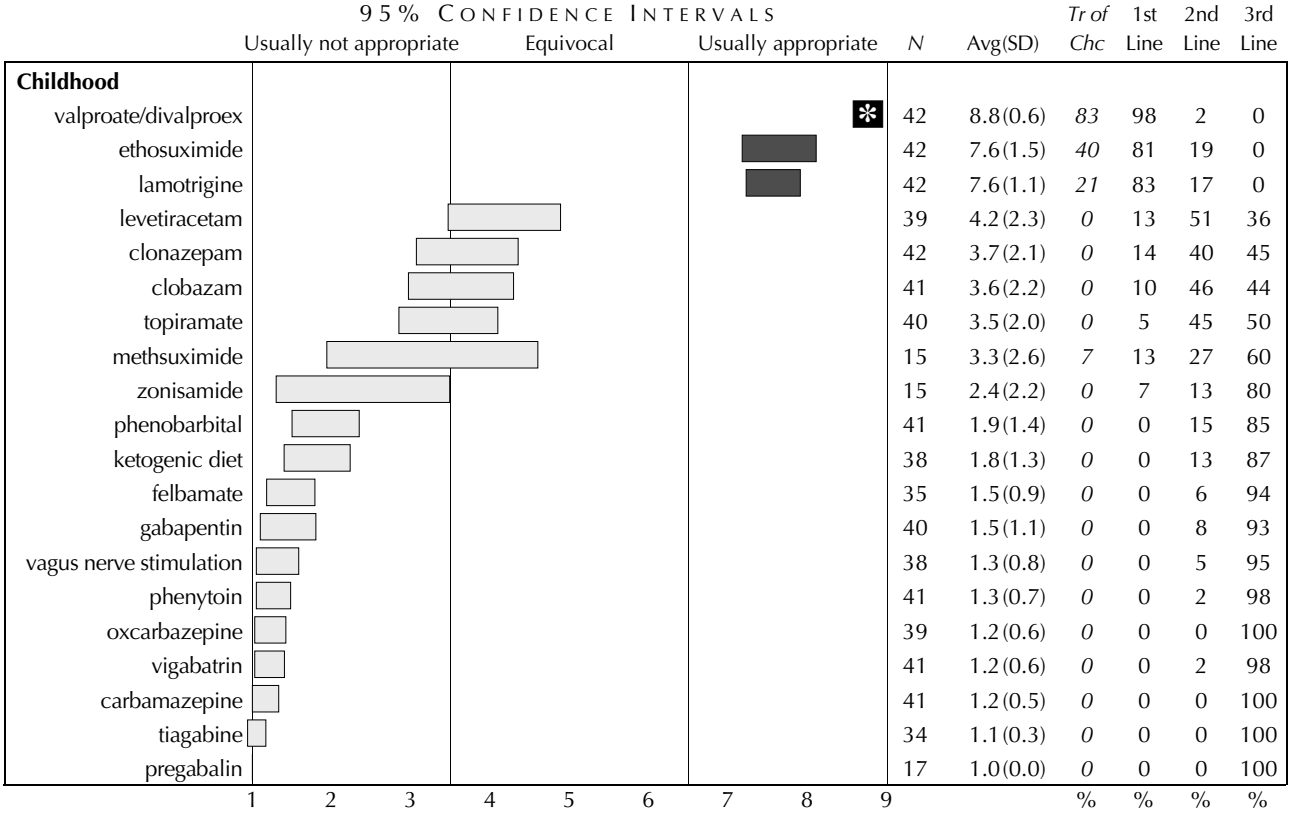
Usually appropriate	Sometimes appropriate*
Valproate	Carbamazepine

*Equivocal but high second-line ratings.
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

8. Absence epilepsy

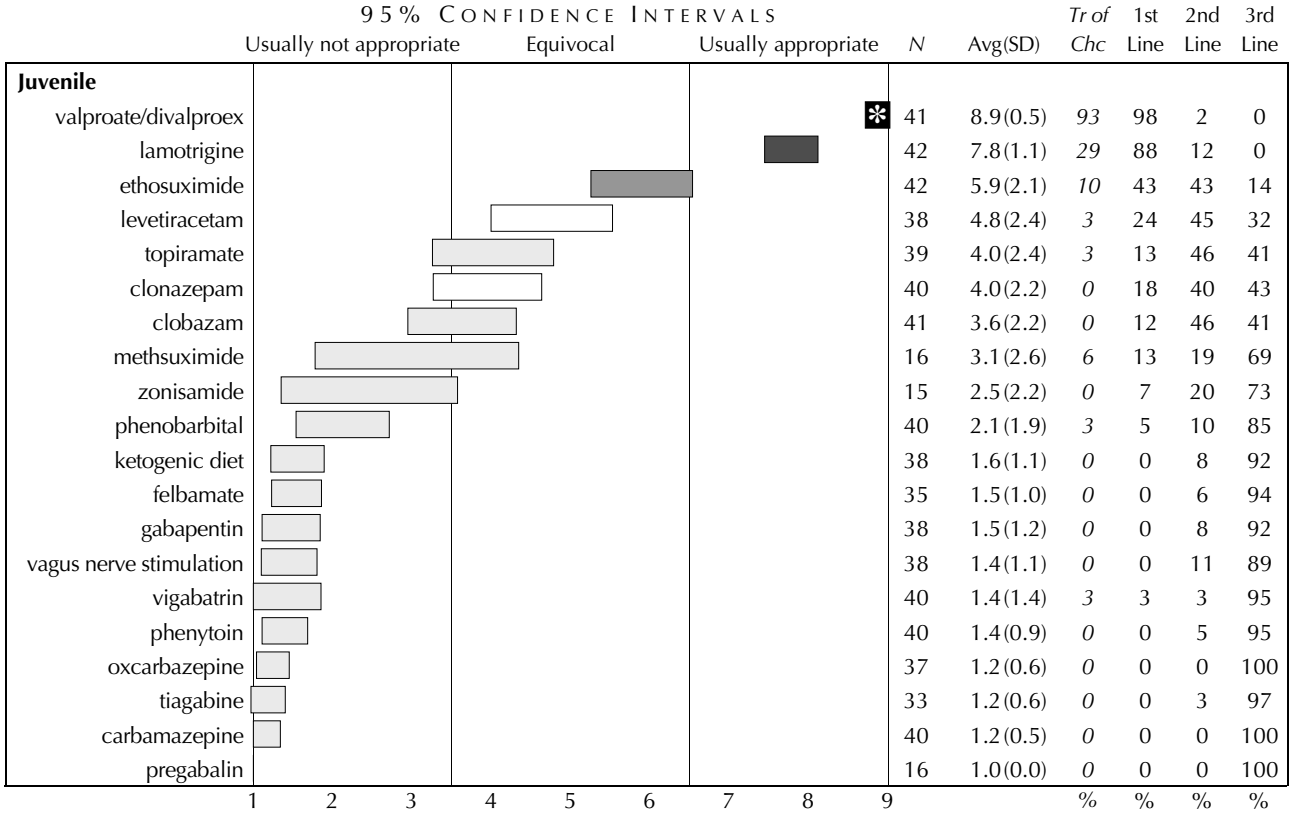
8A. Survey results

Question 27. A healthy 6-year-old is diagnosed with ***childhood absence epilepsy*** (absence seizures only) or ***a healthy 12-year-old*** is diagnosed with ***juvenile absence epilepsy*** (absence and generalized tonic-clonic seizures). The patient is starting therapy for the first time. Assume that you begin with monotherapy. Also assume the parents are amenable to all possible therapies and will be compliant. Please keep in mind the seizure type(s) the child is experiencing (within the syndrome diagnosis), and rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Childhood						
valproate/divalproex	42	8.8(0.6)	*83*	98	2	0
ethosuximide	42	7.6(1.5)	*40*	81	19	0
lamotrigine	42	7.6(1.1)	*21*	83	17	0
levetiracetam	39	4.2(2.3)	*0*	13	51	36
clonazepam	42	3.7(2.1)	*0*	14	40	45
clobazam	41	3.6(2.2)	*0*	10	46	44
topiramate	40	3.5(2.0)	*0*	5	45	50
methsuximide	15	3.3(2.6)	*7*	13	27	60
zonisamide	15	2.4(2.2)	*0*	7	13	80
phenobarbital	41	1.9(1.4)	*0*	0	15	85
ketogenic diet	38	1.8(1.3)	*0*	0	13	87
felbamate	35	1.5(0.9)	*0*	0	6	94
gabapentin	40	1.5(1.1)	*0*	0	8	93
vagus nerve stimulation	38	1.3(0.8)	*0*	0	5	95
phenytoin	41	1.3(0.7)	*0*	0	2	98
oxcarbazepine	39	1.2(0.6)	*0*	0	0	100
vigabatrin	41	1.2(0.6)	*0*	0	2	98
carbamazepine	41	1.2(0.5)	*0*	0	0	100
tiagabine	34	1.1(0.3)	*0*	0	0	100
pregabalin	17	1.0(0.0)	*0*	0	0	100
			%	%	%	%

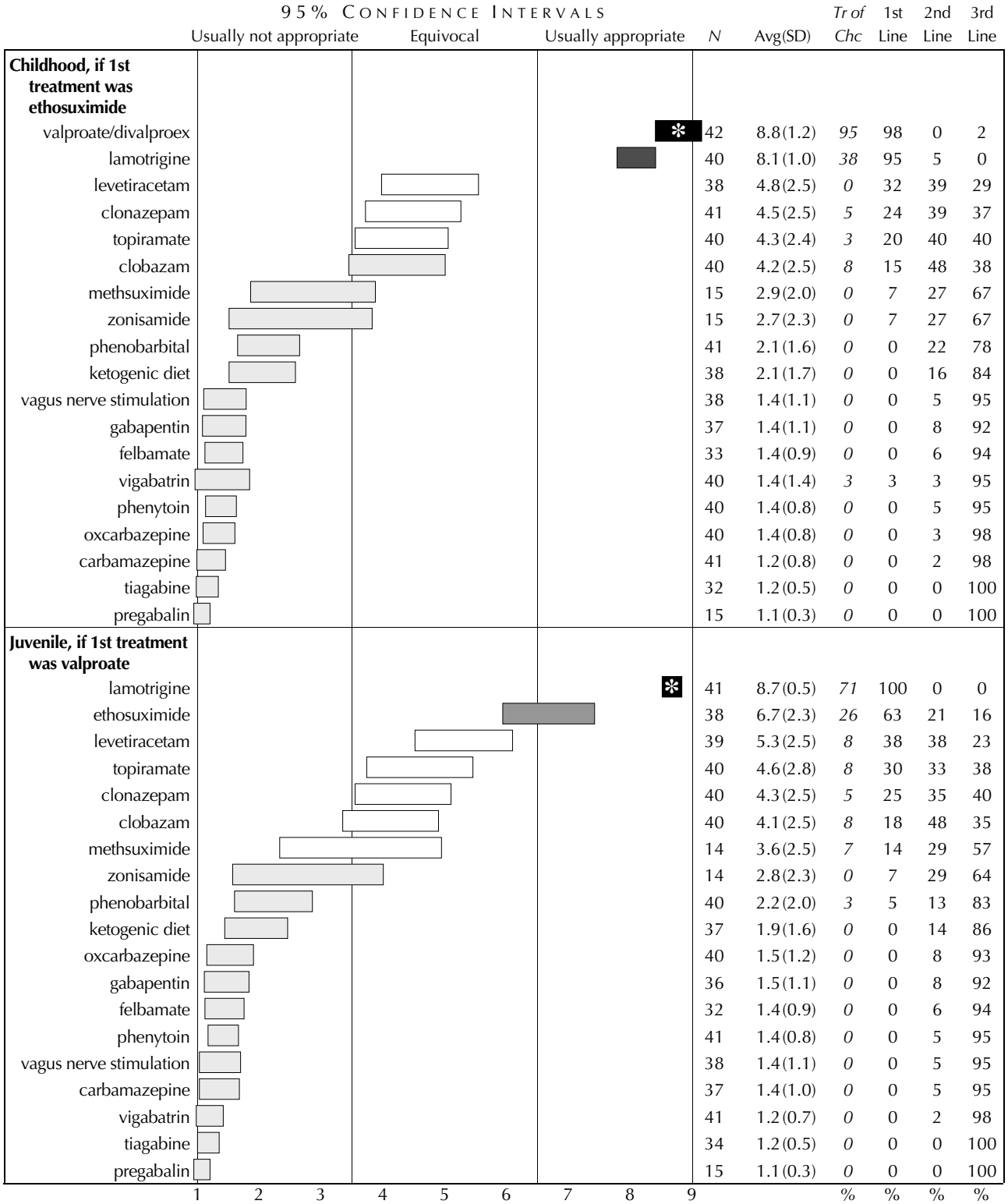
Question 27. *Continued*



Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

Question 28. Assume that the first treatment you choose is ethosuximide for childhood absence epilepsy and valproate for juvenile absence epilepsy. The child either has had no reduction of seizures, a limited response, or the drug was poorly tolerated. Assume you choose a second monotherapy trial. As in question 27, please keep in mind the seizure type(s) the child is experiencing (within the syndrome diagnosis), and rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Childhood, if 1st treatment was ethosuximide						
valproate/divalproex	42	8.8(1.2)	*95*	98	0	2
lamotrigine	40	8.1(1.0)	*38*	95	5	0
levetiracetam	38	4.8(2.5)	*0*	32	39	29
clonazepam	41	4.5(2.5)	*5*	24	39	37
topiramate	40	4.3(2.4)	*3*	20	40	40
clobazam	40	4.2(2.5)	*8*	15	48	38
methsuximide	15	2.9(2.0)	*0*	7	27	67
zonisamide	15	2.7(2.3)	*0*	7	27	67
phenobarbital	41	2.1(1.6)	*0*	0	22	78
ketogenic diet	38	2.1(1.7)	*0*	0	16	84
vagus nerve stimulation	38	1.4(1.1)	*0*	0	5	95
gabapentin	37	1.4(1.1)	*0*	0	8	92
felbamate	33	1.4(0.9)	*0*	0	6	94
vigabatrin	40	1.4(1.4)	*3*	3	3	95
phenytoin	40	1.4(0.8)	*0*	0	5	95
oxcarbazepine	40	1.4(0.8)	*0*	0	3	98
carbamazepine	41	1.2(0.8)	*0*	0	2	98
tiagabine	32	1.2(0.5)	*0*	0	0	100
pregabalin	15	1.1(0.3)	*0*	0	0	100
Juvenile, if 1st treatment was valproate						
lamotrigine	41	8.7(0.5)	*71*	100	0	0
ethosuximide	38	6.7(2.3)	*26*	63	21	16
levetiracetam	39	5.3(2.5)	*8*	38	38	23
topiramate	40	4.6(2.8)	*8*	30	33	38
clonazepam	40	4.3(2.5)	*5*	25	35	40
clobazam	40	4.1(2.5)	*8*	18	48	35
methsuximide	14	3.6(2.5)	*7*	14	29	57
zonisamide	14	2.8(2.3)	*0*	7	29	64
phenobarbital	40	2.2(2.0)	*3*	5	13	83
ketogenic diet	37	1.9(1.6)	*0*	0	14	86
oxcarbazepine	40	1.5(1.2)	*0*	0	8	93
gabapentin	36	1.5(1.1)	*0*	0	8	92
felbamate	32	1.4(0.9)	*0*	0	6	94
phenytoin	41	1.4(0.8)	*0*	0	5	95
vagus nerve stimulation	38	1.4(1.1)	*0*	0	5	95
carbamazepine	37	1.4(1.0)	*0*	0	5	95
vigabatrin	41	1.2(0.7)	*0*	0	2	98
tiagabine	34	1.2(0.5)	*0*	0	0	100
pregabalin	15	1.1(0.3)	*0*	0	0	100
			%	%	%	%

8B. Medication recommendations for absence epilepsy

Valproate was rated as treatment of choice for childhood absence epilepsy, with ethosuximide and lamotrigine other first-line therapies. If initial therapy with ethosuximide failed, then the experts considered valproate treatment of choice and lamotrigine another first-line therapy as the next option. A recent Cochrane review (Posner *et al.* 2003) concluded that, while ethosuximide, lamotrigine, and valproate "are commonly used to treat children with absence seizures, we have insufficient evidence to inform clinical practice" and that "more trials of better quality are needed." In July, 2004, the National Institute of Health (NIH) approved the largest clinical trial to date in pediatric epilepsy (National Institute of Neurological Disorders 2004). This is a multicenter, randomized, double-blind study to investigate the efficacy and side-effect profile of ethosuximide, lamotrigine, and valproic acid in childhood absence epilepsy. This 5-year study will determine which of these three treatments is really the best for this common childhood epilepsy. Although open-label trials of zonisamide and topiramate have suggested that these two broad-spectrum antiepileptic drugs may have efficacy in childhood absence epilepsy (Wilfong and Schultz 2005, Cross 2002). They were rated as usually not appropriate by the expert panel.

Valproate was rated as treatments of choice with lamotrigine another first-line option for juvenile absence epilepsy, reflecting their efficacy for both absence and generalized tonic-clonic seizures. Unlike in childhood absence epilepsy, ethosuximide was not rated first line for juvenile absence epilepsy due to its lack of efficacy in generalized tonic-clonic seizures. If a child has failed to respond to valproate, lamotrigine was rated treatment of choice as the next option, with ethosuximide considered sometimes appropriate (high second-line option).

The 2003 national French survey endorsed valproate as the treatment of choice for absence epilepsy in men and in women not considering pregnancy and endorsed lamotrigine as treatment of choice for women of childbearing age considering pregnancy (Semah *et al.* 2004). (Note that no distinction was made in this survey as to whether it was childhood absence epilepsy or juvenile absence epilepsy.) Lamotrigine is the only new antiepileptic drug recommended by the American Academy of Neurology and the American Epilepsy Society for the treatment of newly diagnosed absence seizures (French *et al.* 2004a). This is consistent with the recent recommendations from the Scottish Intercollegiate Guidelines Network (2005) that support the use of valproate, ethosuximide, or lamotrigine for absence epilepsy in children.

Age	Clinical situation	Usually appropriate	Sometimes appropriate*
Child	Initial monotherapy	***Valproate*** Ethosuximide Lamotrigine	—
	Second monotherapy after failure of initial trial of ethosuximide	***Valproate*** Lamotrigine	—
Juvenile	Initial monotherapy	***Valproate*** Lamotrigine	Ethosuximide
	Second monotherapy after failure of initial trial of valproate	***Lamotrigine***	Ethosuximide

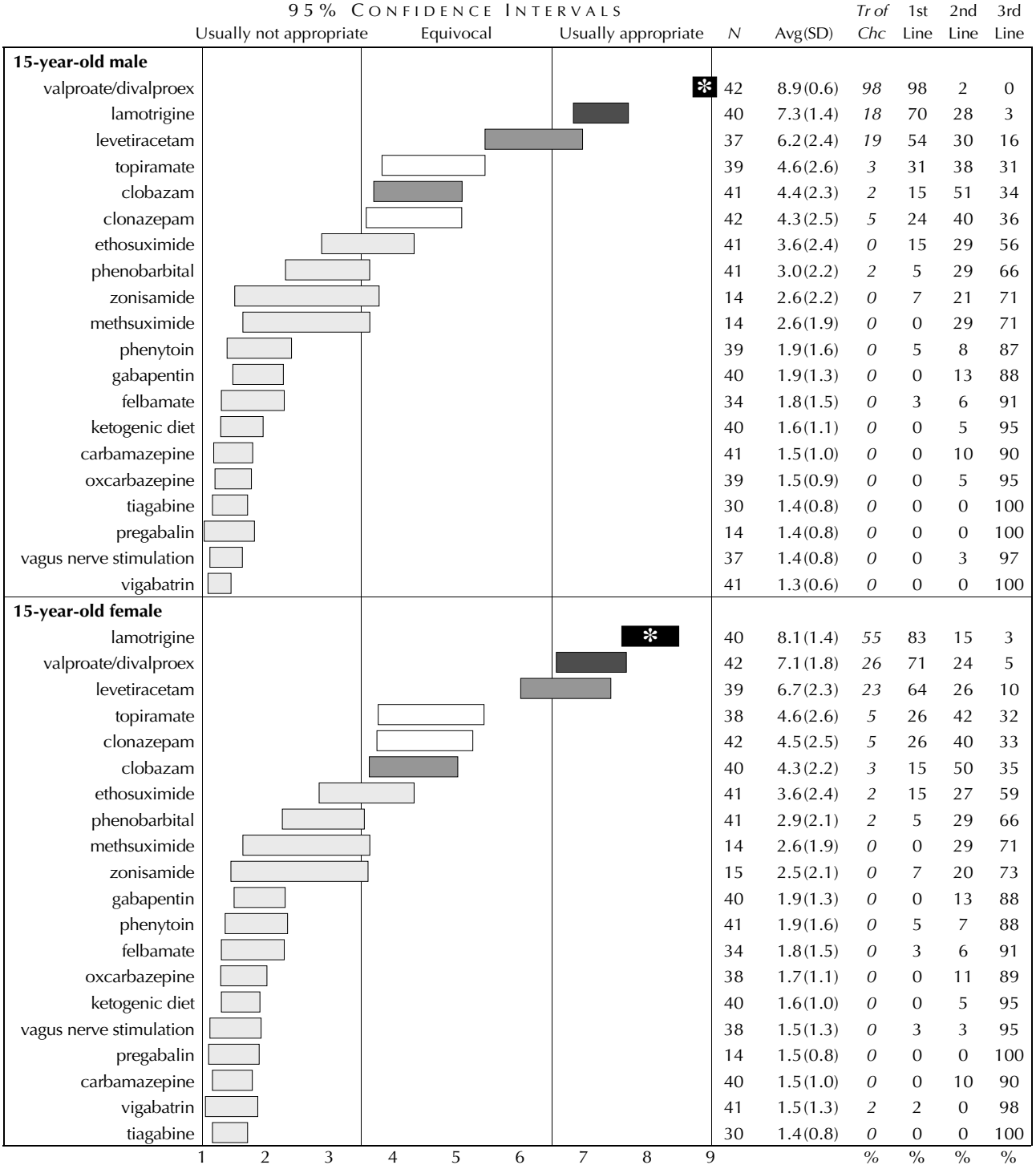
*Equivocal but high second-line ratings.

Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

9. Juvenile myoclonic epilepsy

9A. Survey results

Question 33. A healthy adolescent (male or female) is diagnosed with ***juvenile myoclonic epilepsy (JME)***. The patient is being treated for the first time. Assume that you begin with monotherapy. Assume that the parents are amenable to all possible therapies and will be compliant. Please keep in mind the epilepsy syndrome the adolescent has and rate the appropriateness of each of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
15-year-old male						
valproate/divalproex	42	8.9(0.6)	*98*	98	2	0
lamotrigine	40	7.3(1.4)	*18*	70	28	3
levetiracetam	37	6.2(2.4)	*19*	54	30	16
topiramate	39	4.6(2.6)	*3*	31	38	31
clobazam	41	4.4(2.3)	*2*	15	51	34
clonazepam	42	4.3(2.5)	*5*	24	40	36
ethosuximide	41	3.6(2.4)	*0*	15	29	56
phenobarbital	41	3.0(2.2)	*2*	5	29	66
zonisamide	14	2.6(2.2)	*0*	7	21	71
methsuximide	14	2.6(1.9)	*0*	0	29	71
phenytoin	39	1.9(1.6)	*0*	5	8	87
gabapentin	40	1.9(1.3)	*0*	0	13	88
felbamate	34	1.8(1.5)	*0*	3	6	91
ketogenic diet	40	1.6(1.1)	*0*	0	5	95
carbamazepine	41	1.5(1.0)	*0*	0	10	90
oxcarbazepine	39	1.5(0.9)	*0*	0	5	95
tiagabine	30	1.4(0.8)	*0*	0	0	100
pregabalin	14	1.4(0.8)	*0*	0	0	100
vagus nerve stimulation	37	1.4(0.8)	*0*	0	3	97
vigabatrin	41	1.3(0.6)	*0*	0	0	100
15-year-old female						
lamotrigine	40	8.1(1.4)	*55*	83	15	3
valproate/divalproex	42	7.1(1.8)	*26*	71	24	5
levetiracetam	39	6.7(2.3)	*23*	64	26	10
topiramate	38	4.6(2.6)	*5*	26	42	32
clonazepam	42	4.5(2.5)	*5*	26	40	33
clobazam	40	4.3(2.2)	*3*	15	50	35
ethosuximide	41	3.6(2.4)	*2*	15	27	59
phenobarbital	41	2.9(2.1)	*2*	5	29	66
methsuximide	14	2.6(1.9)	*0*	0	29	71
zonisamide	15	2.5(2.1)	*0*	7	20	73
gabapentin	40	1.9(1.3)	*0*	0	13	88
phenytoin	41	1.9(1.6)	*0*	5	7	88
felbamate	34	1.8(1.5)	*0*	3	6	91
oxcarbazepine	38	1.7(1.1)	*0*	0	11	89
ketogenic diet	40	1.6(1.0)	*0*	0	5	95
vagus nerve stimulation	38	1.5(1.3)	*0*	3	3	95
pregabalin	14	1.5(0.8)	*0*	0	0	100
carbamazepine	40	1.5(1.0)	*0*	0	10	90
vigabatrin	41	1.5(1.3)	*2*	2	0	98
tiagabine	30	1.4(0.8)	*0*	0	0	100
			%	%	%	%

9B. Medication recommendations for juvenile myoclonic epilepsy

Valproate was the treatment of choice for JME in adolescent males and lamotrigine was another first-line option, whereas lamotrigine was treatment of choice in adolescent females, with valproate also first line. Levetiracetam was rated as sometimes appropriate (high second line) in both sexes. This rating probably reflects results of recent studies that have shown that levetiracetam has efficacy as adjunctive therapy in JME and idiopathic generalized epilepsy, resulting in labeling changes in the United States and Europe (Andermann *et al.* 2005, Berkovic *et al.* 2007). A recent report also suggests the efficacy of levetiracetam monotherapy in JME (Sharpe *et al.* 2007). The difference in ratings of valproate for males versus females probably reflects valproate's known teratogenicity (Alsdorf and Wyszynski 2005, Artama *et al.* 2005, Samren *et al.* 1997, Wyszynski *et al.* 2005) and the recent concern that *in utero* exposure to valproate could have potential harmful effects on the infant's neuropsychological development (Adab *et al.* 2004, Eriksson *et al.* 2005, Vinten *et al.* 2005). However, even with these concerns, valproate is still considered a first-line choice in adolescent females, reflecting the historical use of this medication and its efficacy in treating JME (Asconape and Penry 1984, Delgado-Escueta and Enrile-Bacsal 1984, Penry *et al.* 1989, Sullivan and Dlugos 2004). Valproate continues to be rated as the most effective agent in the treatment of JME and idiopathic generalized seizures, a view supported by two recent review articles (Koutroumanidis *et al.* 2005, Verrotti *et al.* 2006) and supported by the recent SANAD randomized controlled trial (Marson *et al.* 2007b). In addition, newer studies that have examined the efficacy of lamotrigine, topiramate, and valproate in JME have all shown that valproate has the best efficacy of the three (Mohanraj and Brodie 2005, 2007, Nicolson *et al.* 2004, Prasad *et al.* 2003). While topiramate was another first-line option in both sexes in the U.S. survey (Wheless *et al.* 2005), there was no consensus on topiramate, which received lower second-line ratings from the European panel. This may reflect the limited controlled studies with topiramate in the treatment of JME and its greater efficacy for generalized tonic-clonic seizures compared with myoclonic and absence seizures (where there was no statistical difference from placebo) (Biton *et al.* 2005). Open-label studies suggest that zonisamide has efficacy in the treatment of JME (Kothare *et al.* 2004, Wheless and Bourgeois 2004) and the experts on pediatric epilepsy who completed the U.S. survey rated zonisamide as high second line (Wheless *et al.* 2005). The third-line rating by European experts likely reflects lack of familiarity with this antiepileptic drug (only 15 experts rated this option in question 33), the limited availability of zonisamide in Europe at the time this survey was done, and the lack of controlled studies.

The 2001 and 2005 expert consensus surveys on adult epilepsies (Karceski *et al.* 2001, 2005) ranked valproate as the treatment of choice for idiopathic generalized epilepsy when the patient's sex was not specified. However, in the 2005 survey on adult epilepsy, when it was specified that the patient was a woman with idiopathic generalized epilepsy, the experts rated lamotrigine as treatment of choice, just as the experts in our survey did. The Scottish guidelines (Scottish Intercollegiate Guidelines Network 2005) noted only evidence from case series to support the use of valproate, topiramate, and lamotrigine as monotherapy in JME. In the National French survey concerning newly diagnosed epilepsy, valproate was recommended as treatment of choice and lamotrigine was the second choice for idiopathic generalized epilepsy in males, while lamotrigine was treatment of choice and valproate was the second choice in females (Semah *et al.* 2004). Topiramate and levetiracetam were the third and fourth choices for idiopathic generalized epilepsy in the French survey. These results are generally consistent with the recommendations of the experts in our survey, reflecting an apparent consensus of opinion regarding medical therapy in this epilepsy syndrome, even though no placebo-controlled, randomized trials have been reported in newly diagnosed patients with JME since the original description by Janz (Grunewald and Panayiotopoulos 1993, Janz 1989).

Patient	Usually appropriate	Sometimes appropriate*
15-year old male	***Valproate*** Lamotrigine	Levetiracetam
15-year old female	***Lamotrigine*** Valproate	Levetiracetam

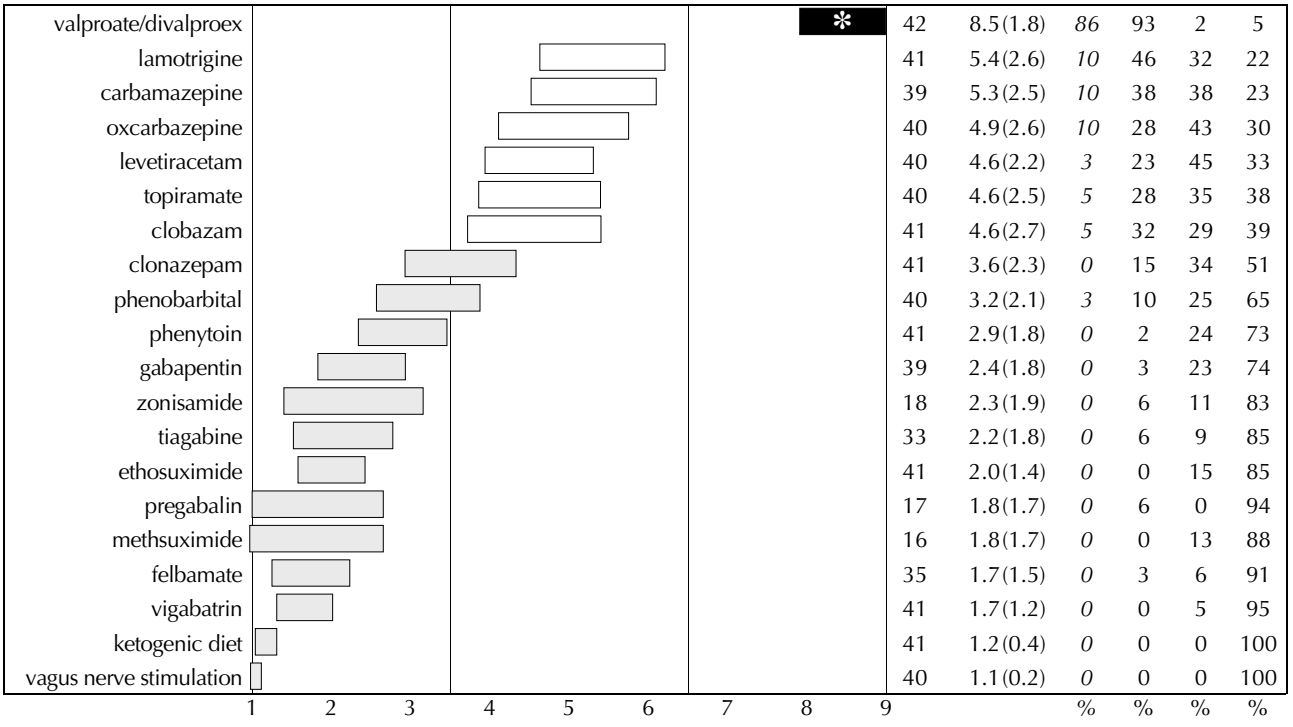
*Equivocal but high second-line ratings.

Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

10. Newly diagnosed epilepsy in the emergency department

10A. Survey results

Question 18. In this question, assume that ***a healthy 6-year-old*** has just arrived in the ***emergency department***, having had two or three seizures. Assume that the suspicion for seizure disorder is high; however, the type of seizure and/or epilepsy syndrome is unclear based on available information. The decision is made to start treatment. Please rate the appropriateness of the following treatments.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
valproate/divalproex	42	8.5(1.8)	*86*	93	2	5
lamotrigine	41	5.4(2.6)	*10*	46	32	22
carbamazepine	39	5.3(2.5)	*10*	38	38	23
oxcarbazepine	40	4.9(2.6)	*10*	28	43	30
levetiracetam	40	4.6(2.2)	*3*	23	45	33
topiramate	40	4.6(2.5)	*5*	28	35	38
clobazam	41	4.6(2.7)	*5*	32	29	39
clonazepam	41	3.6(2.3)	*0*	15	34	51
phenobarbital	40	3.2(2.1)	*3*	10	25	65
phenytoin	41	2.9(1.8)	*0*	2	24	73
gabapentin	39	2.4(1.8)	*0*	3	23	74
zonisamide	18	2.3(1.9)	*0*	6	11	83
tiagabine	33	2.2(1.8)	*0*	6	9	85
ethosuximide	41	2.0(1.4)	*0*	0	15	85
pregabalin	17	1.8(1.7)	*0*	6	0	94
methsuximide	16	1.8(1.7)	*0*	0	13	88
felbamate	35	1.7(1.5)	*0*	3	6	91
vigabatrin	41	1.7(1.2)	*0*	0	5	95
ketogenic diet	41	1.2(0.4)	*0*	0	0	100
vagus nerve stimulation	40	1.1(0.2)	*0*	0	0	100
			%	%	%	%

Key

- ✻ Treatment of choice, rated extremely appropriate by ⩾ 50%.
- Usually appropriate or first line.
- Equivocal or second line.
- Usually not appropriate or third line.
- No consensus.

10B. Medication recommendations for newly diagnosed epilepsy in the emergency department

Valproate was considered treatment of choice for a 6-year-old child with new onset seizures. This rating likely reflects the view that valproate is currently the antiepileptic drug with the broadest spectrum of efficacy across all types of seizures and syndromes (Aldenkamp *et al*. 2006), an important consideration in treatment selection when the seizure type is not clear. There was no consensus among the experts on any of the other medications we asked about. While this clinical scenario is not uncommon, it is one that appears to deserve further study.

Only one comparative study of antiepileptic drugs that did not specify seizure type as an entry criterion has been performed in children (Wheless *et al*. 2004a). In this study, carbamazepine, valproate, and topiramate demonstrated equivalent efficacy. Other studies of newly diagnosed childhood epilepsy have typically included only partial-onset (with or without secondary generalization) and generalized tonic-clonic seizures. These studies have shown efficacy for phenobarbital, phenytoin, carbamazepine, valproate, oxcarbazepine, clobazam, and vigabatrin (Canadian Study Group for Childhood Epilepsy 1998, de Silva *et al*. 1996, Guerreiro *et al*. 1997, Mitchell and Chavez 1987, Verity *et al*. 1995, Zamponi and Cardinali 1999). Mohanraj and Brodie (2005) reported on their clinical experience with carbamazepine, lamotrigine, and valproate in adolescents and adults with newly diagnosed epilepsy. In this observational study, the authors reported that lamotrigine produced better response rates for localization-related epilepsy syndromes, while valproate produced the highest response rates in idiopathic generalized epilepsies.

Conventional wisdom dictates selection of a broad-spectrum antiepileptic drug in this situation, providing coverage for both partial and generalized seizures (Semah *et al*. 2004). In the 2003 French national survey (Semah *et al*. 2004), valproate was recommended as the treatment of choice for an adult male with unclassified epilepsy, followed by lamotrigine and topiramate and then levetiracetam as the next choices; for a woman with unclassified epilepsy not considering pregnancy, valproate and lamotrigine were treatments of choice, followed by topiramate and levetiracetam. Carbamazepine was not considered an option for unclassified epilepsy in the recommendations from the French survey (Semah *et al*. 2004). The experts who completed the survey in the United State rated carbamazepine as first line, with oxcarbazepine, valproate, levetiracetam, topiramate, and lamotrigine all rated high second line (Wheless *et al*. 2005). The first-line ratings given to carbamazepine by the U.S. panel probably reflect the perception that the child's seizure was likely partial onset, while the first-line ratings given to valproate by the European experts probably reflect their desire to use an established, broad-spectrum agent when the seizure type is not clear and to avoid medications that could cause seizure exacerbation. Both groups of experts had difficulty selecting an agent to use next, as demonstrated by the lack of consensus on this question concerning many of the antiepileptic drugs among the European experts and the lack of statistical difference between five medications that were rated second line by the U.S. experts.

Usually appropriate	Sometimes appropriate
Valproate	—

Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

11. Status epilepticus

11A. Overall strategy

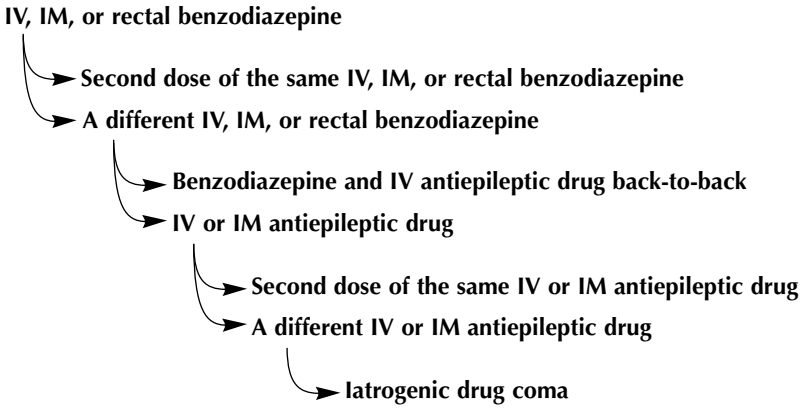
Question 3. A 4-year-old child is in convulsive status epilepticus. No treatment has been started. Assume each treatment is given appropriately and tried to maximum dose.

		n for each step					
Therapy	**Total *N***	**1**	**2**	**3**	**4**	**5**	**Avg**
Sublingual benzodiazepine	6	6					1.00
IV, IM or rectal benzodiazepine	42	39	3				1.07
Second dose of same IV, IM, or rectal benzodiazepine	19		19				2.00
A different IV, IM, or rectal benzodiazepine	18		12	5	1		2.39
Benzodiazepine and an IV AED back-to-back	19		7	9	1	2	2.89
IV or IM AED	34		2	24	8		3.18
Second dose of same IV or IM AED	10			2	6	2	4.00
A different IV or IM AED	31			1	22	8	4.23
Iatrogenic drug coma	30			1	4	25	4.80

AED = antiepileptic drug; IM = intramuscular; IV = intravenous.

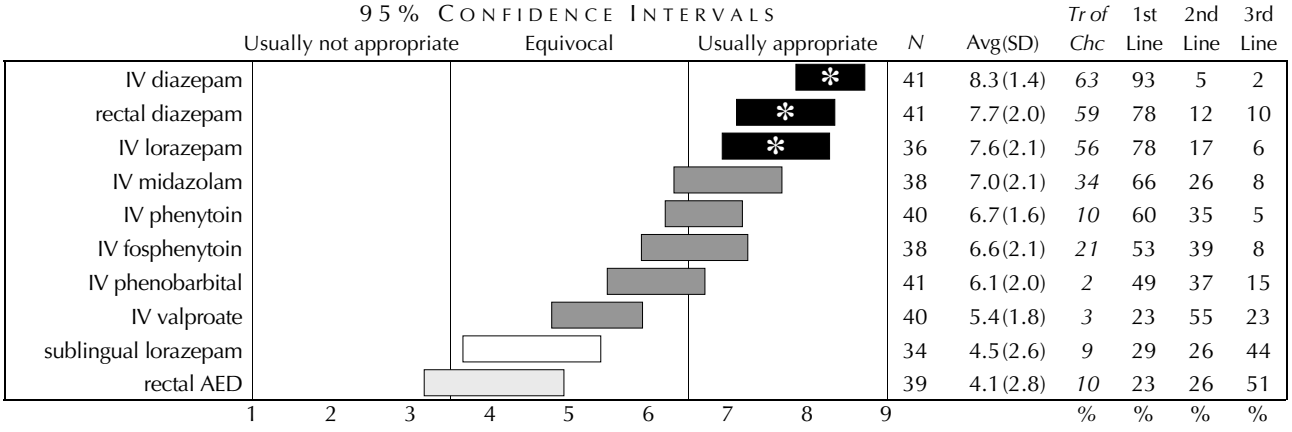
Comment: the experts recommended an IV, IM, or rectal benzodiazepine as the initial treatment for convulsive status epilepticus in a 4-year-old child. For outpatient management of status epilepticus, rectal diazepam has been the standard treatment. An alternative route of administration of benzodiazepines is a buccal or sublingual approach. Recent studies support the efficacy and safety of these methods (McIntyre *et al.* 2005, Scott *et al.* 1999, Scottish Intercollegiate Guideline Network 2005), and this is reflected in the endorsement by a limited number of the experts in our survey (likely reflecting limited availability of a commercial formulation). The next step recommended was to repeat the benzodiazepine dose or try a different benzodiazepine. If the child did not respond to the benzodiazepine alone, they would then try using a benzodiazepine and an IV antiepileptic drug back-to-back or else an IV or IM antiepileptic drug alone. If this was not successful, the experts would then try a different parenteral antiepileptic drug. If none of these medication strategies succeeded, the experts would then consider using an iatrogenic drug coma, This sequence is consistent with that suggested for adults in the 2001 expert consensus survey on adult epilepsy (Karceski *et al.* 2001) (the 2005 survey did not repeat questions on status epilepticus [Karceski *et al.* 2005]), the European Federation of Neurological Societies (EFNS) Guideline on the management of status epilepticus in adults (Meierkord *et al.* 2006), and the initial recommendations of the 2005 Scottish guidelines (Scottish Intercollegiate Guidelines Network 2005). There is no accepted definition of refractory status epilepticus, and no controlled studies have been performed in this area. As a result, surveys of expert opinion on the treatment of refractory status epilepticus show no consensus concerning the number of treatments or the exact sequence of treatments it is appropriate to use before proceeding to anesthetic agents (iatrogenic drug coma) (Claassen *et al.* 2003, Holtkamp *et al.* 2003). This is similar to the recommendations we received in this survey of European experts, who recommended several possible treatment steps before proceeding to iatrogenic drug coma.

However, current reviews that discuss our understanding of the underlying pathophysiological mechanisms of status epilepticus as well as clinical studies suggest that patients are very unlikely to respond to a second standard agent (typically phenobarbital) if the first agent fails to produce a response (Bleck 2002, Lowenstein 2005). As a result, there is growing recognition that more aggressive therapies (e.g., earlier use of iatrogenic coma) are likely to be required if patients do not respond to initial treatment with standard first-line agents (Meierkord *et al.* 2006).



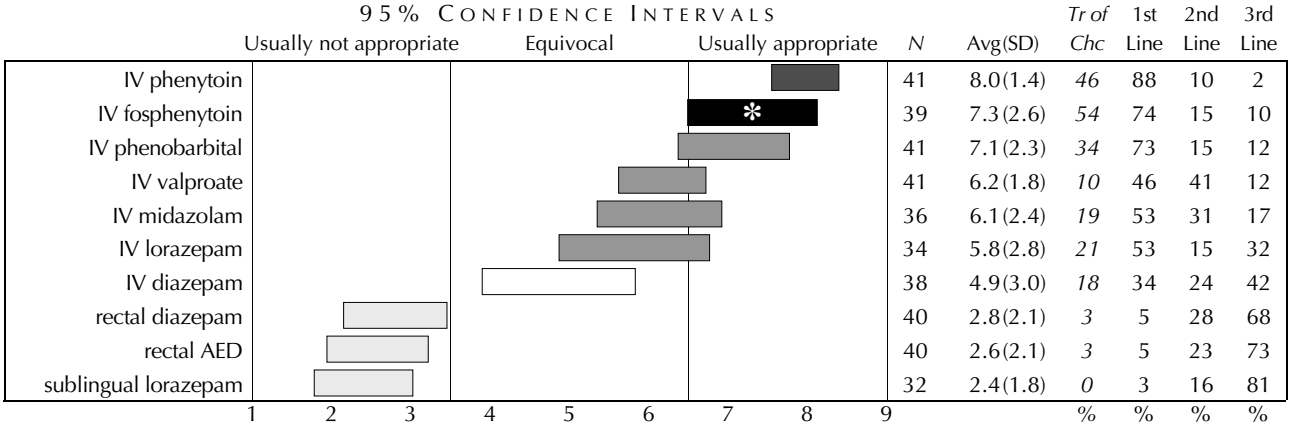
11B. Treatment selection for status epilepticus: survey results

Question 12. A healthy 4-year-old is in ***generalized tonic-clonic status epilepticus***. No treatment has been given yet. Assume that you begin with a single treatment, and assume each treatment is tried to maximum dose. Rate the appropriateness of each of the following treatments.



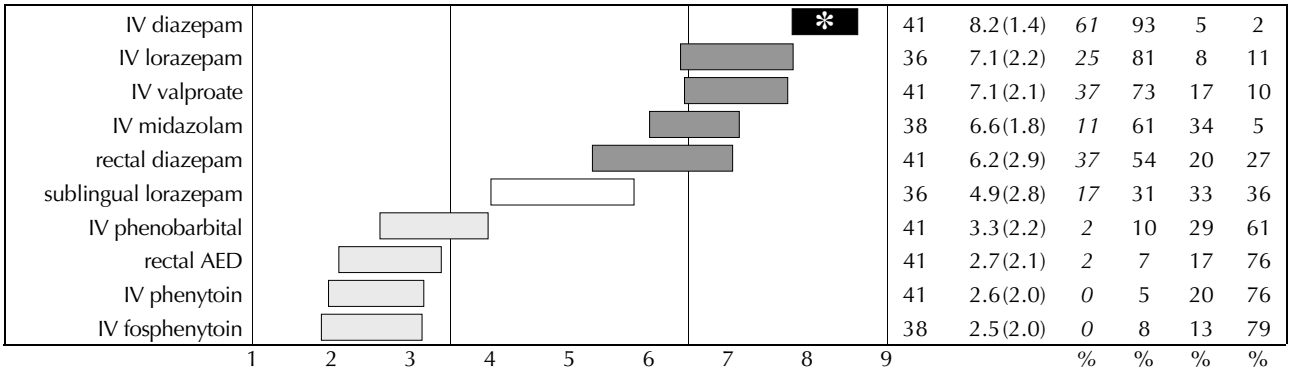
	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
IV diazepam	41	8.3(1.4)	63	93	5	2
rectal diazepam	41	7.7(2.0)	59	78	12	10
IV lorazepam	36	7.6(2.1)	56	78	17	6
IV midazolam	38	7.0(2.1)	34	66	26	8
IV phenytoin	40	6.7(1.6)	10	60	35	5
IV fosphenytoin	38	6.6(2.1)	21	53	39	8
IV phenobarbital	41	6.1(2.0)	2	49	37	15
IV valproate	40	5.4(1.8)	3	23	55	23
sublingual lorazepam	34	4.5(2.6)	9	29	26	44
rectal AED	39	4.1(2.8)	10	23	26	51
			%	%	%	%

Question 13. A healthy 4-year-old is in ***generalized tonic-clonic status epilepticus***. Assume the patient has first been given a benzodiazepine and this has been given to its maximum dose. It has failed to stop the convulsive status epilepticus. As in most clinical situations, the first agent is still on board and the second agent must now be administered. Please rate the appropriateness of the following therapies.



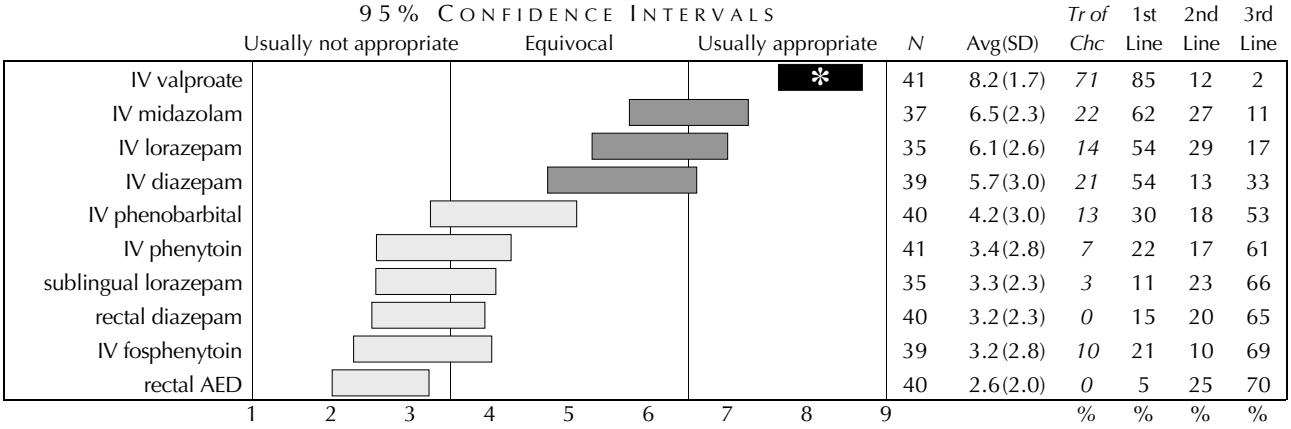
	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
IV phenytoin	41	8.0(1.4)	46	88	10	2
IV fosphenytoin	39	7.3(2.6)	54	74	15	10
IV phenobarbital	41	7.1(2.3)	34	73	15	12
IV valproate	41	6.2(1.8)	10	46	41	12
IV midazolam	36	6.1(2.4)	19	53	31	17
IV lorazepam	34	5.8(2.8)	21	53	15	32
IV diazepam	38	4.9(3.0)	18	34	24	42
rectal diazepam	40	2.8(2.1)	3	5	28	68
rectal AED	40	2.6(2.1)	3	5	23	73
sublingual lorazepam	32	2.4(1.8)	0	3	16	81
			%	%	%	%

Question 14. A healthy 8-year-old is in ***absence status epilepticus***. No treatment has been given yet. What do you give first? Assume the airway is protected.



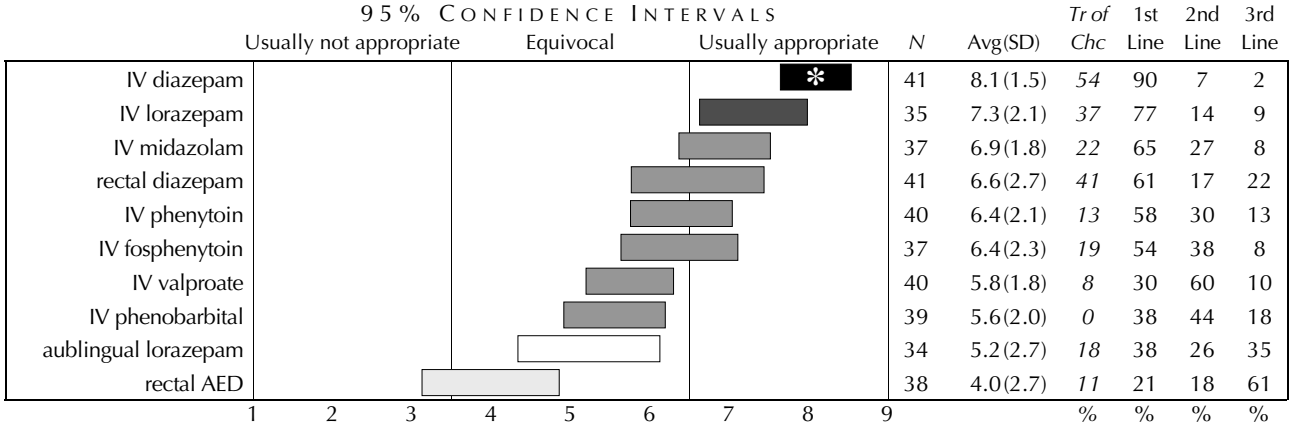
	N	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
IV diazepam	41	8.2(1.4)	61	93	5	2
IV lorazepam	36	7.1(2.2)	25	81	8	11
IV valproate	41	7.1(2.1)	37	73	17	10
IV midazolam	38	6.6(1.8)	11	61	34	5
rectal diazepam	41	6.2(2.9)	37	54	20	27
sublingual lorazepam	36	4.9(2.8)	17	31	33	36
IV phenobarbital	41	3.3(2.2)	2	10	29	61
rectal AED	41	2.7(2.1)	2	7	17	76
IV phenytoin	41	2.6(2.0)	0	5	20	76
IV fosphenytoin	38	2.5(2.0)	0	8	13	79
			%	%	%	%

Question 15. A healthy 8-year-old is in ***absence status epilepticus***. Assume the patient has been first given a benzodiazepine and this has been given to its maximum dose. It has failed to stop the absence status epilepticus. As in most clinical situations, the first agent is still on board and the second agent must now be administered. Please rate the appropriateness of the following therapies. Again, assume that the patient's airway is protected.



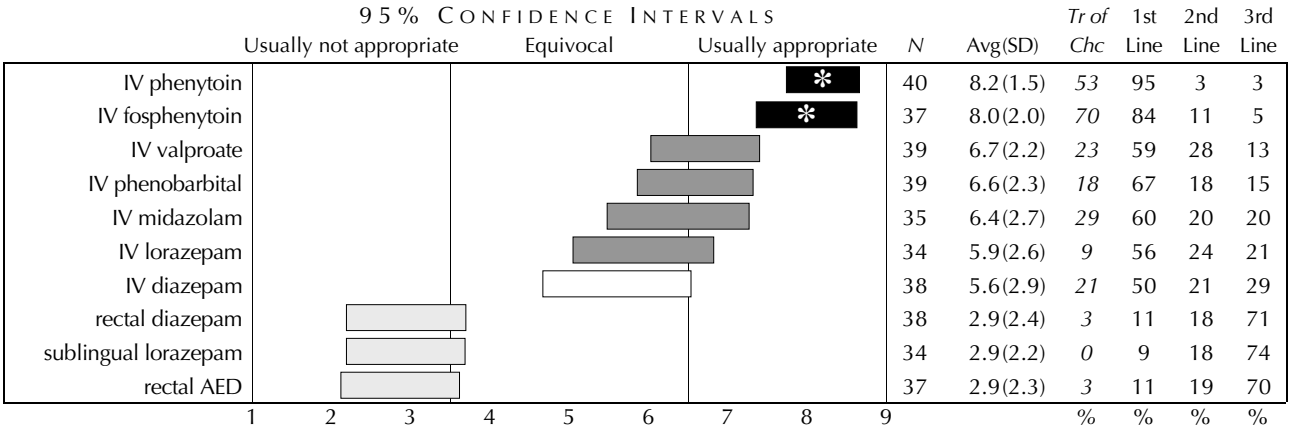
	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
IV valproate	41	8.2(1.7)	*71*	85	12	2
IV midazolam	37	6.5(2.3)	*22*	62	27	11
IV lorazepam	35	6.1(2.6)	*14*	54	29	17
IV diazepam	39	5.7(3.0)	*21*	54	13	33
IV phenobarbital	40	4.2(3.0)	*13*	30	18	53
IV phenytoin	41	3.4(2.8)	*7*	22	17	61
sublingual lorazepam	35	3.3(2.3)	*3*	11	23	66
rectal diazepam	40	3.2(2.3)	*0*	15	20	65
IV fosphenytoin	39	3.2(2.8)	*10*	21	10	69
rectal AED	40	2.6(2.0)	*0*	5	25	70
			%	%	%	%

Question 16. A healthy 6-year-old is in ***complex partial status epilepticus***. No treatment has been given yet. What do you give first? Assume the airway is protected.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
IV diazepam	41	8.1(1.5)	*54*	90	7	2
IV lorazepam	35	7.3(2.1)	*37*	77	14	9
IV midazolam	37	6.9(1.8)	*22*	65	27	8
rectal diazepam	41	6.6(2.7)	*41*	61	17	22
IV phenytoin	40	6.4(2.1)	*13*	58	30	13
IV fosphenytoin	37	6.4(2.3)	*19*	54	38	8
IV valproate	40	5.8(1.8)	*8*	30	60	10
IV phenobarbital	39	5.6(2.0)	*0*	38	44	18
aublingual lorazepam	34	5.2(2.7)	*18*	38	26	35
rectal AED	38	4.0(2.7)	*11*	21	18	61
			%	%	%	%

Question 17. A 6-year old is in ***complex partial status epilepticus***. Assume the patient has been first given a benzodiazepine to its maximum dose. It has failed to stop the status epilepticus. As in most clinical situations, the first agent is still on board and the second agent must now be administered. Please rate the appropriateness of the following treatments. Again, assume that the patient's airway is protected.



	N	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
IV phenytoin	40	8.2(1.5)	*53*	95	3	3
IV fosphenytoin	37	8.0(2.0)	*70*	84	11	5
IV valproate	39	6.7(2.2)	*23*	59	28	13
IV phenobarbital	39	6.6(2.3)	*18*	67	18	15
IV midazolam	35	6.4(2.7)	*29*	60	20	20
IV lorazepam	34	5.9(2.6)	*9*	56	24	21
IV diazepam	38	5.6(2.9)	*21*	50	21	29
rectal diazepam	38	2.9(2.4)	*3*	11	18	71
sublingual lorazepam	34	2.9(2.2)	*0*	9	18	74
rectal AED	37	2.9(2.3)	*3*	11	19	70
			%	%	%	%

11C. Medication recommendations for status epilepticus

IV or rectal diazepam and IV lorazepam were identified as treatments of choice as initial therapy for generalized tonic-clonic status epilepticus in childhood. IV diazepam was also treatment of choice for absence, and complex partial status epilepticus in childhood, with IV lorazepam another first-line choice for complex partial status epilepticus. Lorazepam was identified as the treatment of choice over diazepam in the recommendations in the 2001 expert consensus survey on adult epilepsy (Karceski *et al.* 2001) (note that the 2005 survey did not repeat questions on status epilepticus [Karceski *et al.* 2005]) and in published adult (Lowenstein and Alldredge 1998, Treiman *et al.* 1998) and pediatric (Wheless and Clarke 2005) protocols. This reflects the greater efficacy of lorazepam in adult trials (Lowenstein 2005) and its longer duration of action, potentially allowing initiation of oral therapy after seizure cessation. Interestingly, in support of these survey results, a Cochrane review found no data to support lorazepam having better efficacy than diazepam in children (Appleton *et al.* 2002). The experts who completed the U.S. survey rated benzodiazepines as first-line therapy and selected lorazepam as the treatment of choice, probably reflecting efficacy data on the treatment of adult status epilepticus. The European experts chose a benzodiazepine as first-line therapy and then fosphenytoin or phenytoin as the next choice after initial treatment with benzodiazepines, except for absence status epilepticus, where valproate was recommended as the next therapy after initial treatment with benzodiazepines. These recommendations contrast with those of the U.S. experts, who gave first-line ratings to IV fosphenytoin for complex partial and generalized status epilepticus and first-line ratings to IV valproate for absence status epilepticus. The European experts' recommendations concerning sequencing of therapy (i.e., a benzodiazepine first, followed by a standard antiepileptic drug) probably better reflect current efficacy data gained from treatment of convulsive status epilepticus in adults (Lowenstein 2005, Treiman *et al.* 1998). Fosphenytoin and phenytoin are listed as second monotherapy agents for partial and generalized status epilepticus, likely reflecting the observation that no clinically significant differences between response rates or hypotensive and other adverse cardiac effects associated with phenytoin or fosphenytoin loading have been reported. Given the difference in price, many experts advocate use of fosphenytoin in children, in whom infusion site reactions may be more likely to occur. IV phenytoin is associated with an increased risk of peripheral IV side effects (Wheless 1998). IV valproate was endorsed as second monotherapy after an initial trial of a benzodiazepine only for absence status epilepticus, probably because of valproate's efficacy in treating absence seizures (see page S43). Although no formal trials of valproate have been performed in absence status epilepticus, open-label reports suggest efficacy (Wheless 2003) and it may be given safely by rapid infusion (Venkataraman and Wheless 1999, Wheless and Venkataraman 1998, Wheless *et al.* 2004b, Yu *et al.* 2003) approaching the same administration time as an IV benzodiazepine.

Presentation	Clinical situation	Usually appropriate	Sometimes appropriate*
A healthy 4-year old in generalized tonic-clonic status epilepticus	Initial monotherapy	***IV diazepam*** ***Rectal diazepam*** ***IV lorazepam***	IV midazolam IV phenytoin IV fosphenytoin IV phenobarbital
	Second monotherapy after an initial trial of a benzodiazepine	***IV fosphenytoin*** IV phenytoin	IV phenobarbital IV valproate IV midazolam IV lorazepam
A healthy 8-year-old in absence status epilepticus	Initial monotherapy	***IV diazepam***	IV lorazepam IV valproate IV midazolam Rectal diazepam
	Second monotherapy after an initial trial of a benzodiazepine	***IV valproate***	IV midazolam IV lorazepam IV diazepam
A healthy 6-year-old in complex partial status epilepticus	Initial monotherapy	***IV diazepam*** IV lorazepam	IV midazolam Rectal diazepam IV phenytoin IV fosphenytoin
	Second monotherapy after an initial trial of a benzodiazepine	***IV phenytoin*** ***IV fosphenytoin***	IV valproate IV phenobarbital IV midazolam IV lorazepam

*Equivocal but high second-line ratings; IV = intravenous.
Bold italics = treatment of choice (> 50% of the experts identified the choice as "extremely appropriate," rated 9).

Discussion

New treatments for epilepsy have proliferated over the past 20 years. New medications may soon be available and new devices are being studied and may be ready in the not-too-distant future. Trials are also investigating the utility of new surgical techniques (e.g., gamma knife) in the treatment of intractable partial epilepsy. As treatment options increase, there is renewed hope for improved quality of life for people with epilepsy. However, the larger number of choices presents challenges for physicians in choosing the best treatments for a given individual.

Comparison with other recommendations

To summarize what is known about newer antiepileptic drugs, the American Academy of Neurology developed two evidence-based practice guidelines (French *et al*. 2004a and b) based on a review of over 1 400 articles on treatment of new-onset and refractory epilepsy. For newly diagnosed partial and secondary generalized seizures or refractory partial seizures in children, no recommendations were given. Lamotrigine was given as an option for children with newly diagnosed absence seizures (French *et al*. 2004a). Topiramate was effective as adjunctive therapy for refractory idiopathic generalized tonic-clonic seizures in children; and gabapentin, lamotrigine, oxcarbazepine, and topiramate are effective adjuncts for treatment of refractory partial seizures in children (French *et al*. 2004b). Topiramate and lamotrigine may be used to treat drop attacks associated with Lennox-Gastaut syndrome in children (French *et al*. 2004a). These recommendations do not reflect European- or FDA-approved use of these agents; that is, off-label use of these agents is supported by the literature. These recommendations are now over 3 years old and the American Academy of Neurology is currently reviewing newer studies and is in the process of developing new guidelines The International League Against Epilepsy (ILAE) spent 4 years researching the literature on the treatment of epilepsy in preparing their recent guidelines (Glauser *et al*. 2006). They concluded "It is clear than an alarming lack of well-designed, properly conducted epilepsy RCTs *[randomized controlled trials]* exist, especially for generalized seizures/epilepsies and in children." Expert opinion can be used to identify helpful treatment options to fill this information gap.

Antiepileptic drugs represent the primary treatment option and mainstay of treatment for most children with epilepsy. However, beginning in the mid-1990s, both pediatric (Aso and Watanabe 2000, Camfield and Camfield 1996, Camfield *et al*. 1997, Wirrell *et al*. 2001) and adult (Brodie 2005, Brodie and Kwan 2002, Kwan and Brodie 2000 and 2004a) epilepsy studies of seizure outcome suggested that other treatment options be explored after failure to achieve seizure control with two or three antiepileptic drugs. Nonpharmacologic interventions (vagus nerve stimulation, epilepsy surgery, the ketogenic diet) are typically suggested as therapeutic options after an initial failure of medical management (Renfroe and Wheless 2002, Wheless *et al*. 2001, Wiebe *et al*. 2001). Based on a review by the American Academy of Neurology, vagus nerve stimulation therapy was found to achieve a degree of seizure control comparable to that of the new antiepileptic drugs (Fisher and Handforth 1999). Even with this recognition that refractory epilepsy can be identified early in the course of an epilepsy syndrome and that nonpharmacologic options have an important role to play in treating these children, our experts did not usually recommend a nonpharmacologic treatment until after the fifth step (with the exception of mesial temporal lobe epilepsy) and often not until pharmacological therapy had been exhausted. This points out the need for randomized clinical trials in pediatric epilepsy syndromes to evaluate the best medical management and compare pharmacologic and nonpharmacologic treatment options. Ultimately, such studies will provide the pediatric neurologist with better information on which to base treatment decisions regarding the sequencing of therapies.

The choice of treatment for the various pediatric epilepsies depends on the type of seizure or epilepsy syndrome, underscoring the importance of the international classification (Commission on the Classification and Terminology of the International League Against Epilepsy 1989). Various methods, including regulatory studies, expert opinion, guidelines, and evidence-based reviews, have evaluated medical therapies for common childhood epilepsies (*table 4*). Not all epilepsy syndromes were evaluated as part of the recommendations, or in some cases no recommendations could be made based on the current literature (indicated by "none"). However, in spite of this lack of uniformity, what appears to be emerging is a general consensus as to which drugs are useful for which seizure types or epilepsy syndromes (*table 4*). For the treatment of partial-onset seizures, carbamazepine and oxcarbazepine are consistently recommended by all groups. When treating idiopathic generalized convulsive epilepsies, effective therapies include valproate, lamotrigine, and topiramate, while childhood absence epilepsy is best treated with ethosuximide, valproate, or lamotrigine. Vigabatrin and adrenocorticotropic hormone (ACTH) (or corticosteroids) are the suggested medications for infantile spasms. Lennox-Gastaut syndrome should be treated with valproate, topiramate, or lamotrigine. This apparent consensus can be used as a starting point for future comparative trials to evaluate the efficacy, safety, and pharmacokinetics of commonly used medications in each unique childhood epilepsy syndrome (as in the trial sponsored by the National Institutes of Health in childhood absence epilepsy that is currently underway [National Institute of Neurological Disorders and Stroke]). These studies will

Table 4. Comparison of recommendations for the treatment of pediatric epilepsy.

Seizure type or epilepsy syndrome	U.S. pediatric expert consensus survey[a,b]	European pediatric expert consensus survey[b]	ILAE[c]	SIGN[d]	NICE[e]	French study[f]	FDA approved[g]
Partial-onset	OXC, CBZ	OXC, CBZ	A: OXC; B: none C: CBZ, PB, PHT TPM, VPA	PHT, VPA, CBZ, LTG, TPM, OXC, VGB, CLB	CBZ,VPA, LTG, OXC, TPM	OXC, CBZ, LTG (adult males)	PB, PHT, CBZ, OXC, TPM
BECT	OXC, CBZ	VPA	A, B: none C: CBZ, VPA	Not specifically mentioned	CBZ, OXC, LTG, VPA	Not surveyed	None
Childhood absence epilepsy	ESM	VPA	A, B: none C: ESM, LTG, VPA	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy (JME)	VPA, LTG	VPA	A, B, C: none	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM, LTG, LEV
Lennox-Gastaut syndrome	VPA, TPM	VPA	Not reviewed	Not specifically mentioned	LTG, VPA, TPM	Not surveyed	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	VGB	Not reviewed	Not specifically mentioned	VGB, corticosteroids	Not surveyed	None

ACTH: adrenocorticotropic hormone; BECT: benign childhood epilepsy with centro-temporal spikes; CBZ: carbamazepine; CLB: clobazam; ESM: ethosuximide; FLB: felbamate; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; TPM: topiramate; VPA: valproate; VGB: vigabatrin.

[a] Wheless *et al.* 2005

[b] Drugs rated as treatments of choice listed.

[c] International League Against Epilepsy, 2005 (Glauser *et al.* 2006). Recommendations listed according to levels of evidence supporting the efficacy of the options. Level A: > 1 Class I RCT or > 2 Class II RCTs; Level B: 1 Class II RCT; Level C: > 2 Class III RCTs. A Class I study was defined as a randomized clinical trial (RCT) or meta-analysis of RCTs that meets all the following 6 criteria: primary outcome variable is efficacy or effectiveness; treatment duration: > 48 weeks; double-blind study design; superiority demonstrated or detectable non-inferiority boundary (DNIB) < 20%; study exit not forced; appropriate statistical analysis. A Class II study was defined as a RCT or meta-analysis meeting all the Class I criteria except no superiority was demonstrated and DNIB 21%–30% *or* treatment duration > 24 weeks but < 48 weeks. A Class III study was defined as a RCT not meeting all criteria for any Class I or Class II category: open-label study or DNIB > 30% *or* forced exit criterion. (Note these ratings did not take safety data into consideration.)

[d] Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsies in children and young people: A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; March 2005 (Copies available at http://www.sign.ac.uk/pdf/sign81.pdf).

[e] National Institute for Clinical Excellence, Technology Appraisal Guidance 79, Newer drugs for epilepsy in children (www.nice.org/uk/TA 079 guidance) and Clinical Guideline 20. The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care, October 2004 (www.nice.org/uk/CG020NICE guideline). CBZ, VPA suggested as first choices when appropriate; if they do not benefit the child or are unsuitable, clinician can try newer antiepileptic drugs.

[f] Semah *et al.* 2004

[g] FDA approval for each seizure type or epilepsy syndrome (Thomson PDR 2007). Standard antiepileptic drugs (PB, PHT, CBZ) often have no specific seizure type listed in approval. Newer drugs are listed only if they have a monotherapy approval (except for Lennox-Gastaut syndrome and JME, where listing indicates adjunct therapy) extending into the pediatric age range (< 16 years). Topiramate is approved as monotherapy for the treatment of general epilepsies, including JME. Lamotrigine is approved as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures, including JME. Levetiracetam is indcated as adjunctive therapy in the treatment of myoclonic seizures in patients with JME, and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, including JME.

further refine our treatment of both benign and devastating childhood epilepsy, allowing each child to receive the best therapy early on in his or her course of epilepsy, based on adequately powered, randomized clinical trials.

The expert consensus method

Until then, despite the ever-growing body of literature, in many clinical situations the best treatment approach is not established by evidence from randomized clinical trials (Class I evidence), prospective cohort studies (Class II evidence), or case series or case reports (class IV evidence). In these instances, expert opinion, based on available medical literature plus experience, can be used to identify helpful treatment options. These results can be viewed as a consultation with an epilepsy expert or experts. Expert opinion can be summarized in many ways, all of which contain potential biases. The expert consensus method was chosen to develop the recommendations presented in this document because it minimizes biases by pooling the opinions of a large group of experts and statistically analyzing the results. Unlike other methods where the level of agreement between experts is unclear, the expert consensus method identifies questions on which there is no consensus and presents the results in a concise, easily readable format, providing physicians with information that can be incorporated into their day-to-day clinical practice. The expert consensus method was first described in 1996 (Kahn *et al*. 1996, McEvoy *et al*. 1996). Since then, a number of expert consensus surveys have been completed, most of which explored topics in the field of psychiatry. Surveys have been done on bipolar disorder (Kahn *et al*. 1996, Sachs *et al*. 2000, Keck *et al*. 2004), schizophrenia (McEvoy *et al*. 1996 and 1999), obsessive-compulsive disorder (March *et al*. 1997), agitation in dementia (Alexopoulos *et al*. 1998), posttraumatic stress disorder (Foa *et al*. 1999), psychiatric and behavioral problems in mental retardation (Rush and Frances 2000), attention-deficit/hyperactivity disorder (Conners *et al*. 2001), depression in women (Altshuler *et al*. 2001), behavioral emergencies (Allen *et al*. 2001 and 2005), and use of antipsychotic drugs (Kane *et al*. 2003, Alexopoulos *et al*. 2004). Each survey was conducted in a similar manner: key decision points were identified; a group of experts in the field were surveyed, and the responses were analyzed. In each instance, the method offered a "rapid means to communicate a distillate of expert opinion" (Sachs *et al*. 2000). The survey on adult epilepsy, published in 2001, was the first time the method had been applied to a topic outside psychiatry.

Expert opinion does not replace the medical literature; instead, it acts to supplement that information. The evidence-based reviews by French *et al*. (2004a and b) are extremely important documents; however, they are limited by the information the trials can provide, that is, published articles cannot provide guidance if there are no data in the medical literature. It is in these instances that expert opinion becomes an important resource. The two sources of information can be considered as complementary: where the data in clinical trials cannot answer the question, expert opinion can "fill in the gaps."

Limitations of expert consensus

Although the expert consensus method offers many advantages, it also has limitations. First, the experts may be wrong. This is a problem that plagues all surveys or opinion-driven recommendations. Simply put, the fact that a group of experts agrees does not mean they are correct. Only medical research can validate the opinions of the experts. Expert opinion can also change. As new data become available, the opinions of experts will continue to change, reflecting these advances as well as their experience in the optimal use of these therapies.

Another limitation of this survey is that the opinions reflect the expertise of a group based in Europe. In other parts of the world, where other medicines and therapies may be available, expert opinion may differ. Finally, we mostly asked university faculty for their opinion; practices in a private setting may differ.

Clinical utility of expert consensus

The survey results can be helpful to clinicians in a number of ways. As in a consultation, clinicians should weigh the experts' opinions against other information and consider the many variables that make each case unique. The experts' recommendations do not supersede data in the literature or replace clinical judgment; rather, they suggest options clinicians may wish to consider. In most of the clinical scenarios, the experts identified several first-line therapies, which form a "menu" of appropriate therapies for a given situation. The experts also identified a "menu" of equivocal treatment options: options to be considered when the first-line agents are ineffective or produce toxicity.

Using the survey results, clinicians can compare their own practices against those of a panel of experts. All physicians who treat epilepsy face these clinical situations and will have chosen for themselves an overall strategy and choice of therapy for a particular scenario. Expert opinion may support or refute an individual physician's current practice. Where there is disagreement between the two, the expert recommendation should be considered, remembering that the experts did not unanimously agree on all of the treatment options.

In addition to aiding physician self-assessment, the recommendations reinforce the importance of comparison studies of epilepsy therapies. The growing number of available therapies has heightened the need to identify optimum

treatments for epilepsy syndromes. These studies often require large numbers of patients and long-term follow-up. Improvements in patient care would undoubtedly occur, but only after a long process of data accumulation and dissemination of this information. Yet advances in public health do not always require technological breakthroughs or new data. Immediate gains can be made by increasing the speed with which best clinical practices are implemented. When data are lacking or scant, expert opinion can suggest an optimum treatment. These opinions can be used to identify treatment options to be considered in a specific clinical situation. When making decisions, practitioners may then select an option that is optimal for the specific patient.

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