

COMMENTARY

Core elements of epilepsy diagnosis and management: expert consensus from the Leadership in Epilepsy, Advocacy, and Development (LEAD) faculty

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ABSTRACT

Background: Although epilepsy is relatively common, only a limited number of specialized epilepsy centers exist in the United States. Therefore, epilepsy diagnosis and management frequently occur in the community setting. This can complicate patient management and suboptimal care is a potential concern. Delayed recognition and inadequate treatment increase the risk of subsequent seizures, brain damage, disability, and death from seizure-related injuries. To identify core elements of epilepsy management that should be offered to all patients, the Leadership in Epilepsy, Advocacy, and Development (LEAD) faculty assessed current practical issues and identified practices to improve patient care and outcomes.

Scope: This paper presents a consensus opinion formed from a survey of 26 current LEAD faculty members, who answered 105 questions about epilepsy diagnosis and patient evaluation, treatment decisions, lifelong monitoring, and the management of special patient subgroups. Consensus agreement was concluded when $\geq 50\%$ of the faculty provided the same answer. The results were

compiled and areas of consensus are included in this report. The recommendations provided in this commentary are limited by the scope of the survey.

Findings: Consensus was reached on several minimum standard patient management practices. Primary among these minimum standards of care is the need for diagnosis including a detailed medical history, neurological examination, discussions with caregivers, and diagnostic tests including electroencephalograms and magnetic resonance imaging. As the overall goals of therapy include seizure freedom, minimizing side effects, and improving quality of life and long-term safety, therapy decisions should consider parameters that affect these goals, including potential adverse effects of therapy. Antiepileptic drug selection should consider coexisting conditions for possible exacerbation of disease and potential drug–drug interactions.

Conclusions: The core elements of epilepsy management identified here suggest minimum standards that can be used across all settings to improve consistency and quality of epilepsy diagnosis and care.

*see Table 1, LEAD Faculty

Introduction

Epilepsy is a chronic, life-altering condition affecting 2.7 million people in the United States, with approximately 200 000 new cases diagnosed yearly¹. Although the disease encompasses all age groups, those most likely to be affected include young children and adults aged 65 years and older.

The treatment objective for these patients is to restore normal lifestyle through complete control of seizures, with minimal or no adverse effects². Medical management with antiepileptic drugs (AEDs) is the first-line treatment choice for most patients and, in general, long-term seizure freedom can be achieved by approximately 50% of patients with initial monotherapy²⁻⁴. Achieving this goal for every patient is complicated by the fact that, even though epilepsy is a relatively common condition, the number of specialized epilepsy centers in the United States are inadequate to see all of the patients. Therefore, diagnosis and disease management most frequently occur in the community setting.

Delayed recognition and inadequate treatment are of clinical concern because of the increased risk of subsequent seizures, brain damage, disability, and death from injuries incurred during an event⁵. Achieving consistency in basic diagnostic and treatment parameters across clinical settings is crucially important.

To enhance the care of patients with epilepsy, a group of 28 leading experts in the clinical management of epilepsy was created to form the Leadership in Epilepsy, Advocacy, and Development (LEAD) initiative. The initial step in forming LEAD was identifying Tracy A. Glauser, MD, from the Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, and Raman Sankar, MD, PhD, from the David Geffen School of Medicine at the University of California, Los Angeles, CA, USA. These co-chairs directed the selection of the other faculty members. The criteria used for selection of the LEAD members included academic, clinical practice, and geographic considerations. As shown in Table 1, the resultant LEAD panel consists of nationally recognized neurologists, pediatric

Table 1. LEAD Faculty

Co-Chair	Affiliation	Area of specialty
*Tracy A. Glauser, MD	Cincinnati Children's Hospital Medical Center Cincinnati, Ohio	Pediatric Neurologist/ Epileptologist
Raman Sankar, MD, PhD	David Geffen School of Medicine at UCLA and Mattel Children's Hospital, UCLA, Los Angeles, CA, USA	Pediatric Neurologist/ Epileptologist
Faculty member	Affiliation	Area of specialty
Jacquelyn Bainbridge, PharmD	University of Colorado, Denver Denver, Colorado	Clinical Pharmacist
Martina Bebin, MD, MPA	University of Alabama at Birmingham School of Medicine Birmingham, Alabama	Pediatric Neurologist/ Epileptologist
*Selim R. Benbadis, MD	University of South Florida Tampa, Florida	Neurologist/Epileptologist
Deborah T.C. Cantrell, MD	North Texas Neuroscience Center, PA Irving, Texas	Neurologist/Epileptologist
R. Edward Faught, Jr, MD	University of Alabama at Birmingham School of Medicine Birmingham, Alabama	Neurologist/Epileptologist
Michael Gruenthal, MD, PhD	Albany Medical Center Albany, New York	Neurologist/Epileptologist
Laura L. Hershkowitz, DO	Northshore Clinical Associates Erie, Pennsylvania	Neurologist/Epileptologist
*Gregory L. Holmes, MD	Dartmouth Medical Center Lebanon, New Hampshire	Pediatric Neurologist/ Epileptologist
*Aatif M. Husain, MD	Duke University Medical Center Durham, North Carolina	Neurologist/Epileptologist

(continued)

neurologists, epileptologists, and clinicians from across the United States who are well-respected and well-published in the field of epilepsy. Members of LEAD practice in university, Veterans Administration, and multispecialty settings. The mission of this coalition is to address emerging issues and trends by means of educational programming, thereby advancing the treatment of epilepsy.

This consensus document represents the first step of the LEAD faculty toward their goal of improving patient care and outcomes. Through this report and its *Core Elements of Epilepsy Diagnosis and Patient Management* (Appendix 1) the members of LEAD propose minimum standards that can be implemented by community and academic neurologists, primary care physicians, nurse practitioners, and physician

Table 1. Continued

Faculty member	Affiliation	Area of specialty
David M. Labiner, MD	University of Arizona College of Medicine Tucson, Arizona	Neurologist/Epileptologist
Georgia Montouris, MD	Boston University School of Medicine Boston, Massachusetts	Neurologist/Epileptologist
*Dean K. Naritoku, MD	Southern Illinois University School of Medicine Springfield, Illinois	Neurologist/Epileptologist
*Barbara J. Olson, MD	Pediatric Neurology Associates Nashville, Tennessee	Pediatric Neurologist/ Epileptologist
John M. Pellock, MD	Virginia Commonwealth University Richmond, Virginia	Pediatric Neurologist/ Epileptologist
*Patricia E. Penovich, MD	Minnesota Epilepsy Group, PA St. Paul, Minnesota	Neurologist/Epileptologist
Michael D. Privitera, MD	University of Cincinnati Medical Center Cincinnati, Ohio	Neurologist/Epileptologist
*R. Eugene Ramsay, MD	University of Miami School of Medicine Miami, Florida	Neurologist/Epileptologist
*Jong M. Rho, MD	Barrow Neurological Institute and St. Joseph's Hospital & Medical Center Phoenix, Arizona	Pediatric Neurologist/ Epileptologist
*Karen C. Richards, MD	Specially for Children Austin, Texas	Pediatric Neurologist/ Epileptologist
William E. Rosenfeld, MD	The Comprehensive Epilepsy Care Center for Children and Adults St Louis, Missouri	Neurologist/Epileptologist
Jeremy D. Slater, MD	University of Texas Houston, Texas	Neurologist/Epileptologist
Michael C. Smith, MD	Rush Epilepsy Center, Rush University Medical Center Chicago, Illinois	Neurologist/Epileptologist
*Mark C. Spitz, MD	University of Colorado, Denver Denver, Colorado	Neurologist/Epileptologist
*John M. Stern, MA, MD	David Geffen School of Medicine at University of California, Los Angeles Los Angeles, California	Neurologist/Epileptologist
David Vossler, MD	Washington Neuroscience Institute Renton, Washington	Neurologist/Epileptologist
James W. Wheless, MD	University of Tennessee Health Science Center LeBonheur Children's Medical Center St Jude Children's Research Hospital Memphis, Tennessee	Pediatric Neurologist/ Epileptologist

*Member of the LEAD subcommittee on minimum standards of care

assistants to help address the quality and consistency of diagnosis and care to patients with epilepsy. Specifically, these expert guidelines offer recommendations for clinical decision-making in terms of diagnosis, treatment, ongoing monitoring, and lifetime patient management, as well as the management of patient subgroups with special needs.

These recommendations are based on consensus answers from a survey of the LEAD faculty. The recommendations provide best practice guidelines that the LEAD faculty believes physicians should consider as core elements in outpatient diagnosis and management of patients with epilepsy.

Methods

Development of a questionnaire to elicit current considerations regarding minimum standard care of patients with epilepsy was designed by the co-chairs of the LEAD faculty. An outline for the consensus questionnaire was reviewed by four members of LEAD. Based on this review, a draft questionnaire was developed. The final questionnaire consisted of 105 questions, divided into subsections on patient diagnosis and patient evaluation, epilepsy treatment and monitoring, and the treatment and monitoring of special patient subgroups. The primary focus of the questionnaire was on the care of patients with new onset seizures, although care of and referral of refractory patients was also considered in the longer-term management sections. The questionnaire (Appendix 2) was completed by all LEAD faculty and included multiple-choice and check-box questions, and open-ended questions that allowed the LEAD faculty to supply specific answers.

The questionnaire was administered electronically via a secure online survey site from May 1 through June 30, 2007 to the LEAD faculty. There were 26 respondents and two members served as adjudicators. Although the specific responses from each individual were captured in the data collection, the answers were anonymously pooled for analysis as a whole and by

subspecialty where applicable. A consensus was concluded when $\geq 50\%$ of LEAD faculty chose or volunteered the same answer to a given question. In cases where many choices accrued $< 50\%$ to any one choice, responses were included if they were selected by 5 or more LEAD faculty. The consensus summary presented here was prepared using the results of this questionnaire and was subsequently reviewed and edited by the LEAD subcommittee on the minimum standards of care in epilepsy.

Patient diagnosis and evaluation

The LEAD faculty reached a consensus regarding the basic components of patient diagnosis and evaluation, as shown in Figure 1. These basic components set proposed minimum standards of care that should be offered to all patients. Chief among these is the need to obtain basic information about the patient and his or her seizures and to perform the necessary diagnostic tests to guide treatment decisions (Table 2). The consensus of the LEAD faculty is that if these proposed minimum standards for patient evaluation are followed, more accurate diagnosis of absence, partial

Table 2. Clinical practice parameters: patient diagnosis and evaluation. Optimal patient diagnosis and evaluation involves a number of critical components, including a detailed medical history, neurologic and physical examinations, and interviews, as well as diagnostic studies with EEG and MRI

Minimum Recommended Components of Patient Diagnosis and Evaluation

- Detailed medical history
- Neurologic examination
- Physical examination
- Discussion with caregivers
- EEG and MRI

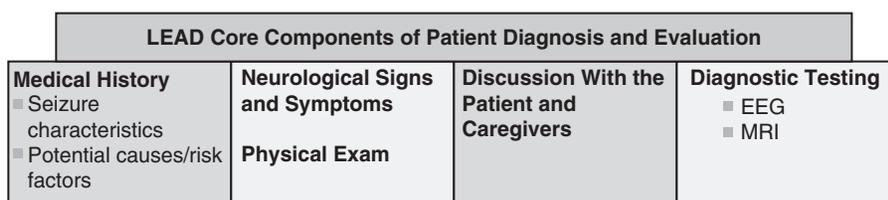


Figure 1. LEAD consensus recommendations: patient diagnosis and evaluation. The proposed LEAD minimum standards of care that should be offered to all patients include the need to obtain basic information about the patient and his or her seizures and to perform the necessary diagnostic tests to guide treatment decisions

onset, generalized, and myoclonic seizures would result (Figure 1).

The specific minimum standards of care recommendations for a medical history, physical and neurological examinations, discussion with the patient and caregivers, and diagnostic testing recommended by the LEAD faculty are summarized in the following sections (Table 2).

Medical history

Determining the seizure details is the first component of the medical history for diagnosis and evaluation of epilepsy. LEAD faculty consensus is that to arrive at the correct diagnosis, the seizure characteristics listed

below should always be determined (% , No. LEAD faculty):

- Was there a warning prior to the seizure? (100%, 26/26)
- Were there any triggers before the seizure? (100%, 26/26)
- Was awareness altered? (100%, 26/26)
- Was motor activity associated with the seizure? (100%, 26/26)
- Have the patient describe his or her feelings before and after the seizure. (100%, 26/26)
- Determine when the seizure(s) occurred. (100%, 26/26)
- Were any automatisms present? (92%, 24/26)

In practice, seizure characteristics can be elucidated by asking the questions provided in Table 3.

Table 3. Core questions for assessing the seizure (% , No. of LEAD Faculty)

Seizure incident characteristic	Questions to ask
Warning prior to the seizure	<ul style="list-style-type: none"> • Did patient experience: <ul style="list-style-type: none"> – Visual aura (92%, 24/26) – Sensory aura (92%, 24/26) – Déjà vu (88%, 23/26) – Tingling fingers (62%, 16/26)
Seizure triggers	<ul style="list-style-type: none"> • Were there any triggers? <ul style="list-style-type: none"> – Sleep deprivation (100%, 26/26) – Flashing lights (96%, 25/26) – Illicit drugs (96%, 25/26) – Alcohol use (92%, 24/26) – Menstrual cycle (92%, 24/26) – Illness (88%, 23/26)
Altered awareness	<ul style="list-style-type: none"> • Did the patient experience: <ul style="list-style-type: none"> – Loss of awareness (100%, 26/26) – Confusion states (100%, 26/26) – Lost track of time (100%, 26/26)
Motor activity associated with seizure	<ul style="list-style-type: none"> • Were there: <ul style="list-style-type: none"> – Abnormal movements; if so, on which side of body (100%, 26/26) – Generalized convulsive movements (100%, 26/26) – Drop attacks (88%, 23/26) – Transient focal motor attacks (88%, 23/26) – Facial muscle or eye movement (88%, 23/26) – Jerks/myoclonic jerks (88%, 23/26) – Episodic phenomena during sleep (77%, 20/26)
Feelings surrounding seizure	<ul style="list-style-type: none"> • Describe feelings before (100%, 26/26), during (88%, 23/26), and after (100%, 26/26) the seizure
Timing of seizure	<ul style="list-style-type: none"> • When did seizure occur? <ul style="list-style-type: none"> – Upon awakening (92%, 24/26) – During sleep (85%, 22/26) – Catamenial (81%, 21/26)

Beyond the characteristics of the seizure itself, a number of other factors require consideration while obtaining the medical history. At a minimum, the following areas should be covered during the process of taking the medical history: (% , No. of LEAD faculty):

- Personal history of seizures (100%, 26/26)
- Medical history (96%, 25/26)
- Risk factors (96%, 25/26)
- Social history (88%, 23/26)

The LEAD faculty consensus is that the key questions presented in Table 4 should be asked to elucidate the four topics above while taking the patient's medical history.

A review of the potential neurological signs and symptoms of epilepsy is another core component of the medical history. During seizure evaluation, many signs and symptoms detailed in Table 5 were listed by the LEAD experts to be most highly relevant to the diagnosis and evaluation of patients with epilepsy.

Discussion with caregivers

To obtain the necessary information for diagnosis, the LEAD faculty agreed that, in addition to taking the

Table 5. *Relevant neurological signs or symptoms to assess*

Condition	% (No.) of LEAD Faculty
Memory problems	81% (21/26)
Headache	81% (21/26)
Lethargy	73% (19/26)
Tremors	73% (19/26)
Incoordination	69% (18/26)
Difficulty walking	69% (18/26)
Double vision	62% (16/26)
Rash	62% (16/26)
Blurred vision	58% (15/26)
Weakness	58% (15/26)
Dysarthria	54% (14/26)
Extreme irritability	54% (14/26)
Vertigo	50% (13/26)

Table 4. *Additional relevant medical history (% , No. of LEAD Faculty)*

Category	Questions
Personal seizure history	<ul style="list-style-type: none"> • Did the patient experience a head injury? (100%, 26/26) <ul style="list-style-type: none"> – Determine if there was any loss of consciousness (100%, 26/26) • When was seizure onset and in what setting? (100%, 26/26) <ul style="list-style-type: none"> – Upon awakening (96%, 25/26) – Asleep (96%, 25/26) – During activity (77%, 20/26) • What is the frequency of seizures? (100%, 26/26) • If seizure free, for how long and while on or off medications? (100%, 26/26) • Did the patient ever experience febrile seizures? (96%, 25/26) • Is the patient aware of any birth injury or trauma during delivery? (92%, 24/26) • Were congenital causes determined? (88%, 23/26)
Medical history	<ul style="list-style-type: none"> • Was anything irregular regarding birth history? (81%, 21/26) • Were there any major or recent hospitalizations or surgeries? (81%, 21/26) • Were there any accidents or recent travel? (77%, 20/26) • Are there any allergies? (65%, 17/26)
Social history	<ul style="list-style-type: none"> • What is the level of education? (85%, 22/26) • Was there normal progression through educational grade level? (81%, 21/26) • What is the patient's occupation? (81%, 21/26) • Does the patient hold a driver's license? (73%, 19/26) • What is the patient's marital status? (54%, 14/26)
Risk factors	<ul style="list-style-type: none"> • What is the family history of seizure? (96%, 25/26) <ul style="list-style-type: none"> – Who (96%, 25/26) – At what age did the seizures end (92%, 24/26) – When (77%, 20/26) • Is there a history of premature birth or neonatal intensive care unit stay of longer than 1 month? (88%, 23/26)

patient's medical history and performing a neurological examination, discussions with the patient's family or caregiver are necessary (100%, 100%, 96% of LEAD members, respectively).

Family and caregivers may be able to explain details of the seizure of which the patient is unaware or unable to convey. Therefore, in addition to patient interviews, caregivers should also be part of the diagnosis and evaluation process. As the treatment plan develops, caregivers are also important to therapy adherence and ongoing patient monitoring, particularly if the patient is or becomes disabled. In addition to family members, group home staff, sponsors, and personal aides are of great importance in the execution of epilepsy management plans for many patients⁶.

Diagnostic tests

The members of LEAD agreed that the diagnostic tests shown in Table 6 are the recommended minimum standard in obtaining an accurate diagnosis. The use of an electroencephalogram (EEG) and magnetic resonance imaging (MRI) is vital for proper diagnosis, with 96%, 25/26 LEAD faculty specifying the need for an EEG and 81%, 21/26 specifying the need for an MRI (Table 6).

The LEAD consensus recommendations on patient diagnosis and evaluation provide a clinical perspective

Table 6. Diagnostics tests to obtain (% , No. of LEAD Faculty)

Diagnostic study	Type
EEG	The EEG should include the following: <ul style="list-style-type: none"> • Awake portion (100%, 26/26), • Using activation procedures (88%, 23/26) • Hyperventilation (88%, 23/26), • Asleep portion (85%, 22/26) • Photic stimulation (85%, 22/26) • Drowsy portion (69%, 18/26)
MRI	MRI (81%, 21/26) <ul style="list-style-type: none"> • MRI with epilepsy protocol (65%, 17/26)

to the current literature in the field, which confirms that the clinical presentation of epilepsy depends on a number of core factors⁷. These consensus recommendations provide a foundation for consistent diagnosis and evaluation of patients with epilepsy. However, they may not include all routine components due to inadvertent omission of items such as basic laboratory assessment from the questionnaire.

Chief among the core factors in epilepsy evaluation are the pathophysiology and affected brain area, the spread or propagation of epileptic abnormality, and the age of the individual⁷. Seizure type has been established to be based on characteristic signs and symptoms. A detailed description of the events before, during, and after the seizure should be routinely obtained by interviewing the patient and any witnesses⁷. In addition, most recommendations and standards include complementary tests with an EEG to confirm seizure type and an MRI to confirm etiology. However, healthcare professionals should appreciate that EEG readings of people with epilepsy may show no abnormality and should consider a diagnosis of a nonepileptic event during the patient evaluation including physiologic and psychologic events^{7,8}. Thus, four basic steps should be followed in the diagnosis and evaluation of patients with epilepsy⁸ (Figure 2).

Epilepsy treatment decisions

The LEAD faculty reached consensus on the minimum standards for a number of epilepsy treatment decisions in terms of initiating, changing, or discontinuing an AED treatment, the principal factors involved in AED selection, such as seizure type and comorbidities, and potential drug–drug interactions (Figure 3). Details of these conclusions are provided in the following sections.

Treatment initiation

The consensus of the LEAD experts is that AED treatment for epilepsy should be initiated after two seizures. Some variability existed in the exact determination of these events among the LEAD faculty in that some

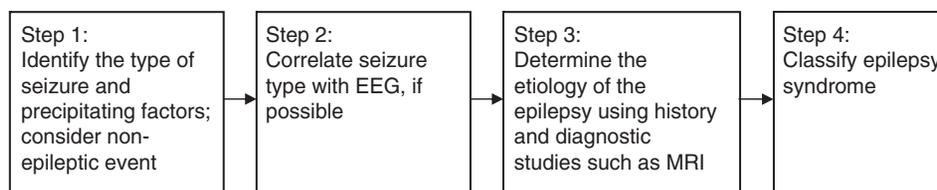


Figure 2. Steps in diagnosis of epilepsy. The diagnosis of epilepsy involves acquiring information about the seizure and the circumstances of its occurrence, as well as the etiology and classification of the epilepsy syndrome

LEAD Core Components of Epilepsy Treatment Decisions			
Treatment Initiation <ul style="list-style-type: none"> Generally after 2 seizures 	Selecting an Optimal AED <ul style="list-style-type: none"> Consider coexisting conditions Consider potential drug-drug interactions Implications of epilepsy syndrome/seizure type 	Consider Changing or Discontinuing AED <ul style="list-style-type: none"> Adverse events Emerging coexisting conditions Drug-drug interactions New epilepsy syndrome Pregnancy Remission 	Additional Decisions and Considerations <ul style="list-style-type: none"> Referral of refractory patients to epilepsy specialist Ketogenic diet for appropriate patients

Figure 3. LEAD consensus recommendations: epilepsy treatment decisions. The proposed LEAD minimum standards of care include basing treatment decisions on factors including seizure type, comorbidities, and potential drug–drug interactions.

Table 7. Principal factors determining AED selection

Key consideration	Evaluate at initial visit % (No. LEAD Faculty)	Evaluate at every visit % (No. LEAD Faculty)
Drug–drug interactions	100% (26/26)	88% (23/26)
Epilepsy syndrome/seizure type	100% (26/26)	81% (21/26)
Comorbidities	100% (26/26)	77% (20/26)
Age of patient	100% (26/26)	65% (17/26)
Long-term health concerns	92% (24/26)	69% (18/26)
Gender	88% (23/26)	54% (14/26)
Teratogenicity	77% (20/26)	54% (14/26)
Ease of use	73% (19/26)	54% (14/26)
Cost	73% (19/26)	50% (13/26)
Idiosyncratic events	65% (17/26)	73% (19/26)
Treatment of emergent adverse events	54% (14/26)	81% (21/26)

believed that these could include two reported seizures (65%, 17/26), some recommended treatment following one witnessed and one reported seizure (42%, 11/26), and some preferred to initiate treatment after two witnessed seizures (35%, 9/26). In some situations AED treatment can be initiated after a single seizure if an abnormal EEG, structural lesion on MRI, or family history is present.

Choosing an optimal AED

The Epilepsy Foundation states that the goals of therapy extend beyond preventing seizures; and the treatment should make it possible for people with epilepsy to lead active lives⁹. Side effects must be minimized, quality of life improved, and long-term safety achieved. The LEAD faculty did not form a consensus opinion on a minimum recommendation for which AED to choose to achieve an optimal outcome for people with epilepsy, but did identify several areas that should be considered when selecting appropriate AED therapy.

These include seizure type, coexisting conditions, and concomitant medications. In everyday practice, most LEAD experts stated that, at a minimum, the top factors to be considered regarding AED selection should include those listed in Table 7.

The LEAD consensus recommendations further establish the need to individualize therapy to accommodate these principal factors. Treatment decisions should be based not only on seizure type and AED efficacy and safety. Rather, the LEAD faculty recommends that decisions should also include additional important considerations. Other relevant factors in treatment decisions include the age and sex of the patient, coexisting conditions, and the potential for emerging conditions and drug–drug interactions^{3,10,11}.

Comorbidities: implications for drug selection

The LEAD experts agreed that the presence of comorbidities has important implications. Table 8 presents

Table 8. Coexisting conditions to consider when determining epilepsy treatment

Condition	% (No. LEAD Faculty)
Developmental delay	85% (22/26)
Depression	73% (19/26)
Behavioral disorder	73% (19/26)
Migraine	69% (18/26)
Cerebral palsy	69% (18/26)
Premature birth	62% (16/26)
Sleep disorder	58% (15/26)
Anxiety disorder	58% (15/26)
Renal disease	54% (14/26)
Bipolar disorder	50% (13/26)
Overweight/obesity	50% (13/26)

the consensus of the LEAD faculty on the comorbid or coexisting conditions that are important to consider when diagnosing a seizure disorder. Other identified conditions selected by <50% of the LEAD faculty were diabetes (12/26), liver disease (12/26), and learning disorder (12/26).

The recommendations from the LEAD faculty highlight the complexity of the full clinical picture in epilepsy and that it may include a variety of comorbidities^{2,12}. Patients are commonly diagnosed with one or more additional neurological, psychiatric, and/or medical disorders. These conditions can interfere with effective epilepsy treatment and daily functioning, and conversely, AED therapy may also affect these associated conditions^{10,13}. Consideration of the relationships among epilepsy, comorbidities, and their treatments is essential to optimal patient management¹⁰.

Impact of drug–drug interaction potential on drug selection

Another necessary consideration in establishing an epilepsy treatment plan is the potential for interactions between AEDs and other medications. All LEAD experts agreed that a given AED's propensity for drug–drug interactions may limit its utility as a first-line agent in the treatment of epilepsy.

Dose adjustments and close monitoring of blood levels and adverse events may be necessary when AEDs are combined. In clinical practice, understanding possible interactions among the various AEDs and other drugs and knowing which AEDs are enzyme inducers and which AEDs are enzyme inhibitors is important. The use of newer AEDs may mitigate some interactions compared with the older AEDs since in general they have fewer potential drug interactions¹⁴. Clinicians

should probe for any changes in medication intake that may occur due to the subsequent onset of comorbid or coexistent conditions.

Epilepsy syndrome/seizure type: implications for therapy

A majority of LEAD faculty (58%, 15/26) felt that although there are areas where there may be an advantage to using a broad-spectrum agent, there was no situation where a broad spectrum of activity is inappropriate. In response to an open-ended question, the LEAD experts generally indicated that broad-spectrum AEDs are a good choice for patients with unknown or unclear seizure types (73%, 19/26).

The LEAD faculty agreed (100%, 26/26) that special consideration in AED selection should be given to patients with absence seizures. In addition, most faculty (73%, 19/26) indicated that consideration in AED selection should be given for patients with myoclonic seizures. Notably, the eight LEAD faculty specializing in childhood neurology who completed the questionnaire also highlighted absence (88%, 7/8), generalized (63%, 5/8), and myoclonic seizures (63%, 5/8) and Lennox-Gastaut syndrome as specific seizure types where particular AEDs may not be appropriate.

Changing or discontinuing AED medications

All LEAD experts (100%, 26/26) agreed that AEDs should be changed due to adverse events (e.g., rash, hepatotoxicity) and a majority of the faculty agreed that AEDs should be changed in the event of poor tolerability (96%, 25/26), the emergence of coexisting conditions leading to contraindication of the AED (96%, 25/26), or in the event of drug–drug interactions (81%, 21/26). Further, more than half of the experts also stated that identification of an epilepsy syndrome (69%, 18/26) and planning or experiencing a pregnancy (65%, 17/26) may also warrant a change in AED therapy.

Most LEAD faculty suggested that therapy should not be discontinued unless adverse events develop, such as hepatotoxicity or rash (65%, 17/26), or there is a strong possibility that the epilepsy has remitted (54%, 14/26). However, there was no consensus among the LEAD experts as to a specific duration that a patient should be seizure free before discontinuation of AED therapy.

Initiating referral to epilepsy specialist

The LEAD faculty agreed that at a minimum, patients should be referred to an epilepsy specialist when they are considered to be refractory or when their treatment

has failed. Most of LEAD (73%, 19/26) believed that the failure of two or more AEDs warranted referral to an epilepsy specialist for further therapy to meet the patient's specific needs.

Ketogenic diet

The LEAD faculty as a whole agreed that a ketogenic diet can be considered in pediatric patients after the failure of two to three or more medications (81%, 21/26) or in cases of intractable seizures. No consensus emerged regarding using the ketogenic diet in any other patient group.

The subgroup of the eight LEAD faculty specializing in childhood neurology who completed the questionnaire noted that this diet should be considered only when the family is committed to following the plan and is able to completely control the diet, and when other appropriate treatments have failed. Furthermore, among the pediatric specialists, it was noted that the ketogenic diet in adolescent patients is a last resort, requiring strong patient and family commitment, and that other options should be tried first.

The LEAD consensus recommendations regarding treatment decisions augment current thinking in the area. The overriding objective of epilepsy treatment is to achieve complete control of seizures, allowing the patient to maintain a normal life, with minimal or limited adverse drug effects. Currently, AED therapy is the initial treatment of choice for most patients, and, in general, long-term seizure freedom can be achieved by approximately 50% of patients with initial monotherapy²⁻⁴.

Although variability exists across age groups and seizure types, approximately 70% to 80% of individuals may ultimately attain seizure freedom with one of the more than 20 AEDs now available, with success rates primarily dependent on the etiology of the seizure disorder^{2,15,16}. Because patients may remain on the initial therapy for several years, the treating physician must select the AED that is, in the physician's opinion, likely to be the most tolerable, with the lowest potential for harm, and has the least likelihood of negatively impacting quality of life based on the unique considerations of each patient¹⁶.

The LEAD experts' identification of the importance of comorbidities in drug selection is consistent with previous work that established that the presence of coexistent medical or psychiatric conditions must be factored into the treatment selection process⁷. For example, migraine headache is a known comorbidity of epilepsy, occurring more often than chance would predict in this population¹⁷. The same is true for depression and dysthymia^{18,19}. Accordingly, any

proposed therapy for epilepsy must take into account other drugs needed to treat comorbidities, both in terms of possible drug-drug interactions as well as the potential for exacerbating the comorbid disorder. Additionally, it may be beneficial to simplify both drug regimens in cases where the comorbid disorder affects adherence, as may occur with psychiatric illnesses.

Monitoring patients with epilepsy and lifetime management of epilepsy

The LEAD faculty did not achieve consensus regarding the specific monitoring and lifetime management of patients with epilepsy, emphasizing the relevance of individual patient situations and characteristics. Although the consensus was that periodic efficacy evaluations based primarily on seizure frequency are necessary and that monitoring for adverse events should occur at each visit, the faculty arrived at few unanimous firm recommendations in terms of specific timing or tests. Similarly, suggestions for methods of regular patient monitoring and counseling were varied, although firm recommendations emerged regarding potential drug interactions and comorbid conditions, weight, body mass index, and specific potential adverse effects of therapy. Overall, a repeated theme in the survey results was the need to assess the monitoring of each patient based on individual needs and events, which may change throughout the patient's lifetime.

Routine clinical and laboratory monitoring

The consensus among the LEAD experts regarding routine monitoring was that the frequency of periodic re-evaluations is primarily based on seizure frequency and on the occurrence of adverse events (88%, 23/26 and 69%, 18/26, respectively). However, no consensus was reached regarding the frequency and specific tests to be routinely followed. Although 100% (26/26) of LEAD faculty believed that such tests were important, specific parameters for monitoring liver function, electrolytes, complete blood counts, sodium bicarbonate levels, and blood levels, and which patients and which agents required specific monitoring, were believed to be discretionary.

Monitoring treatment efficacy

In response to an open-ended question, seizure frequency was volunteered most often by LEAD faculty

as the preferred method of monitoring AED efficacy and was suggested by 35% (9/26) of the faculty. No consensus emerged for scheduling efficacy monitoring, and respondents suggested that efficacy monitoring may be dependent on clinical picture and physician judgment.

Monitoring adverse events

The consensus of the LEAD faculty is that tolerability should be assessed at each visit, with 96% (25/26) of the members citing this as a minimum standard. The LEAD experts agreed that this can be done through interviews with the patient and family (85%, 22/26). Some of the common adverse events to look for with AED therapy that were mentioned by five or more LEAD faculty are provided in Table 9. Most LEAD faculty generally agreed that the recommended management of these adverse events is primarily to adjust the dose, timing, or schedule of the AED administration (69%, 18/26), or to change or discontinue the agent (58%, 15/26).

Patient counseling

While a patient is undergoing AED therapy, a number of potential medical, physical, social, and lifestyle concerns should be discussed during follow-up visits and ongoing patient monitoring. These issues can affect not only ongoing treatment considerations, but also patient quality of life. The consensus was that, at a minimum, the clinician should be prepared to counsel the patient regarding some of these potential concerns as shown in Table 10.

In addition to counseling by the medical care team, other options for support, such as epilepsy support groups, were suggested by 77%, 20/26 of the LEAD faculty; personal and family counseling were suggested by 58%, 15/26 and 38%, 10/26, respectively.

The LEAD faculty agreed that minimum counseling following discontinuation of AED therapy should include advising patients about what to do if seizures recur (88%, 23/26) and the need to continue to adhere to therapy for any comorbid conditions (62%, 16/26).

Although no consensus was reached regarding core recommendations for routine monitoring of patients with epilepsy, the LEAD findings support the importance of individualizing patient management based on patient characteristics and needs. Established guidelines indicate that continuing AED therapy should be planned based on the specific drug choices, dosages, and possible side effects^{8,20}. Specific monitoring, such as AED blood levels, may be added in the event that nonadherence to the prescribed medication regimen is

Table 9. Adverse events to monitor mentioned by ≥ 5 LEAD Faculty

Event to monitor	% (No. LEAD Faculty)
Cognitive slowing or changes, difficulty concentrating	42% (11/26)
Skin and hair changes, rash	27% (7/26)
Emotional changes, mood or personality changes, depression	23% (6/26)
Ataxia	23% (6/26)
Diplopia	23% (6/26)
Sedation or drowsiness	19% (5/26)
Physical fatigue, lethargy	19% (5/26)
Weight increases or decreases	19% (5/26)

Table 10. Issues requiring counseling during follow-up visits

Issue for discussion	% (No. LEAD Faculty)
Women of childbearing age/women's health issues	100% (26/26)
Adverse events	96% (25/26)
Significant coexisting conditions requiring attention	96% (25/26)
Driving	96% (25/26)
Medication adherence	96% (25/26)
Plan for seizure or seizure emergency	92% (24/26)
Bone health	88% (23/26)
Safety during recreational activity	88% (23/26)
Seizure frequency	88% (23/26)
Drug-drug interactions	85% (22/26)
Cognition	77% (20/26)
Sleep problems	69% (18/26)

suspected or if toxicity or seizure breakthrough occurs⁸. In general, patients with well-controlled seizures may need to be seen twice per year or annually, while those with less well-controlled seizures may need to be seen more frequently, depending on the individual situation.

Treatment and monitoring of special patient subgroups

The LEAD faculty reviewed several special patient subgroups potentially having specific needs that impact the selection of therapy and patient management. These

subgroups include women, older patients, pediatric patients, and those with developmental disabilities. Within these subgroups, minimum standards for patient management were agreed on by the faculty, and specific issues and concerns were raised.

Women

Although no unanimous consensus was reached among the LEAD faculty regarding specific monitoring of women and women during pregnancy, some items were repeatedly suggested in response to an open-ended question. Specifically, 73%, 19/26 of the LEAD experts suggested that, at a minimum, women may require additional consideration of teratogenic potential of AED therapy, and the faculty suggested additional monitoring for potential interactions between AEDs and oral contraceptives or steroids.

With respect to frequency of follow-up of women of childbearing age, over half the LEAD faculty (58%, 15/26) agreed that 6- to 12-month routine follow-up is adequate if seizures are well controlled, if there is a known contraceptive method used, and if there are no changes in the patient's condition.

The LEAD faculty's concerns regarding women of childbearing age and pregnancy are consistent with the unique issues surrounding epilepsy in these patients. Women with epilepsy require additional consideration with respect to contraception, pregnancy, and hormone replacement therapy. The choice of AED in these patients may depend on potential interactions with oral contraceptives, teratogenicity of the AED, and cosmetic side effects⁴. Other issues to be considered are the potential for increased seizure frequency during pregnancy, frequency of follow up during the pregnancy, and appropriate breastfeeding. Furthermore, women taking AEDs that induce hepatic enzymes are at increased risk for breakthrough bleeding and oral contraceptive failure due to accelerated estrogen metabolism⁴.

Of every 5 000 pregnancies, approximately 20 will occur in women with epilepsy, and pregnancy may be associated with changes in seizure frequency that require alterations in the planned AED treatment. Teratogenicity is also a concern, as fetuses exposed to AEDs are at higher risk for abnormalities, potentially requiring additional monitoring with level II or high-definition ultrasound, which can detect most major structural abnormalities if performed at 18 weeks' gestation. At a minimum, pregnant women may require more frequent monitoring of blood levels, adjustment of dosage during pregnancy and postdelivery, and detailed consideration of certain variables such as infant care.

Elderly

The LEAD consensus indicates that for patients aged 65 years and older, clinicians should consider the impact of concomitant medications on AED treatment. Although a majority consensus was not reached, overall routine monitoring every 6 months was suggested to be adequate for well-controlled older patients by 35% of the LEAD faculty (9/26). A number of faculty members further suggested that the timing of follow-up may need to be adjusted in these patients depending on seizure frequency (5/26) and other medical conditions and treatments that may alter the pharmacokinetics of AED medications (5/26).

Among the LEAD experts, the top five factors involved in selecting treatment for patients aged 65 years and older are listed below. However, aside from other medications and potential interactions, no majority consensus was identified.

- Other medications and potential interactions (69%, 18/26)
- Comorbidities (35%, 9/26)
- Possible need to reduce AED doses (31%, 8/26)
- Price and financial concerns (23%, 6/26)
- Increased susceptibility to adverse events (19%, 5/26)

The LEAD recommendations emphasize two of the commonly cited concerns that comorbid conditions and physiologic changes due to aging have a direct impact on the outcomes in older patients with epilepsy. Comorbid conditions and physiologic changes that accompany aging can increase the risk of seizures and profoundly alter the response to drug therapy²¹. Further, age-related physiologic changes that affect drug concentrations, such as reduced hepatic clearance and renal elimination, may result in the poor tolerability of AEDs in elderly patients. A number of evaluations have indicated that AEDs become less tolerable with increasing age²¹. Older patients typically have a narrower therapeutic window or a smaller range between the lowest effective concentration and the maximum tolerated concentration²². Therefore, elderly patients may, in general, be more susceptible to adverse effects, and these effects may occur at lower AED levels²².

Pediatric patients

Although no consensus was reached regarding special management of pediatric patients as a whole, in response to an open-ended question, a large percentage of the LEAD faculty (42%, 11/26) noted that children can be more tolerant of some AEDs without observable side effects than adults receiving the same dose. Furthermore, a number of LEAD faculty (35%, 9/26)

believed that clinicians should use the lowest effective drug load to seek to reduce central nervous system adverse effects in children.

Among the entire LEAD faculty, the minimum follow-up for well-controlled pediatric patients with no adverse events was recommended to be every 6 months by 54%, 14/26 members.

Although no consensus was reached regarding absolute minimum considerations for modifying treatment in young patients, five or more of the LEAD faculty suggested the following as items to consider in pediatric patients:

- Cognitive effects (31%, 8/26)
- Comorbid conditions (27%, 7/26)
- Potential for neurotoxicity (23%, 6/26)
- Learning/school performance (19%, 5/26)
- Seizure frequency and control (19%, 5/26)
- Age (19%, 5/26)
- Seizure type (19%, 5/26)
- Tolerability of AEDs and adverse events (19%, 5/26)

Although somewhat limited by the open-ended nature of the survey questions and the relatively few pediatric specialists included in the LEAD faculty, the LEAD consensus results emphasize concerns that are well-established for pediatric patients. Treatment of epilepsy in children also requires consideration of development-sensitive factors. Children present a different pharmacokinetic profile from adults, may display age-specific organ toxicities, and may have a different range of psychiatric comorbidities. Further, AED selection can impact behavior and learning²³. As children age and pass through the developmental stages of childhood into adolescence, different comorbid conditions may also develop. Thus, periodic reassessment of dose and choice of medication may be necessary¹⁰.

Patients with developmental disabilities

Although no real consensus was reached, the LEAD faculty survey results indicate that prior response to AEDs, treatment goals, patient anxiety, and level of functioning in the community may be relevant components of epilepsy management in developmentally challenged individuals.

In well-controlled developmentally challenged patients with no adverse events, most LEAD faculty (65%, 17/26) agreed that routine follow-up every 6 months is adequate.

Some basic factors to consider in modifying treatment for patients with developmental disabilities or decreased intellectual capacity that were volunteered

by five or more of the LEAD faculty in response to an open-ended question include:

- Possible increased risk of behavioral adverse effects (31%, 8/26)
- Sedation – avoid drugs that reduce energy level or alertness (19%, 5/26)

Epilepsy is prevalent among groups with disabilities such as autism, cerebral palsy, Down syndrome, and mental retardation. Evidence from several studies suggests that the risk of seizures is clearly elevated in patients with either very severe or multiple disabilities²⁴. Specific challenges in treating these individuals include a higher incidence of medically refractory epilepsy, cognitive disabilities that can limit feasibility of neurodiagnostic testing, and the inability to describe or report symptoms in those with limited communicative ability. In addition, developmentally disabled patients are more likely to experience adverse effects of AEDs⁶. The LEAD consensus regarding the care of patients with developmental disabilities is consistent with current research, indicating that the key to treating these patients is to individualize care while recognizing behavioral, psychiatric, and medical comorbid conditions²⁵. AED selection for these patients should be based on the principles of efficacy, safety, and simplification.

Conclusions

The LEAD faculty, based on the consensus results of a survey, proposes a number of minimum standard patient management practices. Primary among these is arriving at an accurate diagnosis by obtaining a detailed medical history, neurological examination, initiating discussions with caregivers, and diagnostic tests including EEG and MRI. Because the overall goals of therapy include freedom from seizures, minimization of side effects, improved quality of life, and long-term safety, AED therapy must be initiated with consideration of key parameters affecting these goals. To optimize the initial choice of AED, patients' coexisting conditions should be evaluated, both in terms of possible exacerbation of disease or potential drug–drug interactions. Clinicians need to probe for any changes in medication intake that may occur due to the subsequent onset of comorbid or coexistent conditions.

Overall, AEDs are the initial treatment choice for most patients, and treatment is generally initiated after two seizures with impairment. The LEAD experts agreed that broad-spectrum agents should also be considered for cases in which the seizure type is unclear or mixed.

Patients receiving epilepsy therapy require routine monitoring for efficacy and adverse events, as well as changes in their status. AEDs should be changed in response to adverse events, drug–drug interactions, poor tolerability, or the emergence of coexisting conditions leading to contraindication of the AED. Development of a new seizure type or other clinical considerations may also warrant a change in AED therapy.

Certain patient subgroups have unique issues that should be considered in determining AED therapy, including women, older patients, pediatric patients, and patients with developmental disabilities.

In conclusion, the LEAD faculty's consensus is that these minimum standards for basic care should be offered to all patients presenting with a potential diagnosis of epilepsy. These standards should be able to be implemented across clinical settings by a variety of caregivers to provide quality and consistency in the care of patients with epilepsy. The LEAD consensus provides a core structure for clinical decision-making in terms of diagnosis, treatment, ongoing monitoring, and lifetime patient management, as well as the management of patient subgroups with special needs.

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Appendix

The following two appendices are available as electronic supplementary data (doi 10.1185/03007990802561239) published with the online version of this article.

Appendix 1: Core Elements of Epilepsy Diagnosis and Patient Management

Appendix 2: LEAD faculty survey questionnaire

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