SYLLABUS AND COURSE GUIDE

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Epilepsy in the New Millennium: Emerging Treatments and Guidelines for Effective Diagnosis and Disease Management

neuroscience CME

A Free, One-Hour CME/CNE/CEP/NASW/CCMC/CPE WEBCAST

www.neuroscienceCME.com/CM440

FACULTY: Cynthia L. Harden, MD
FACULTY: Michael R. Sperling, MD

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This continuing education activity is co-sponsored by Indiana University School of Medicine and by CME Outfitters, LLC.

INDIANA UNIVERSITY SCHOOL OF MEDICINE

CME Outfitters

This activity is supported by an unrestricted educational grant from Pfizer Inc.

INFORMATION FOR PARTICIPANTS

Statement of Need

Does having a seizure mean epilepsy, or is it an isolated neurological event? Failure to recognize diagnostic uncertainty between the epilepsies and non-epileptic events may be a factor in high rates of misdiagnosis.[1] Many patients who have been misdiagnosed as having epilepsy have had previous EEGs interpreted as epileptiform that contributed to the misdiagnosis of epilepsy.[2] Patients are often faced with the need to tolerate complex cocktails of medications over long periods of time causing side effects of these chronic medications to be of concern for both physicians and their patients. Pharmacologic management of patients with epilepsy is one of the greatest unmet needs of the disease. It is important that clinicians are aware of the evidence for current and emerging therapies so they can individualize care of their patients. There is no real "Gold Standard" of guidelines for improving diagnosis and treatment of epilepsy,[3] but clinicians need to be aware of the most recent guidelines and how they can incorporate them in their practice. In this neuroscienceCME webcast, the experts will explore these clinical challenges of managing patients with epilepsy, and will provide insights and strategies for the improvement of patient care.

1 Beach R, Reading R. The importance of acknowledging clinical uncertainty in the diagnosis of epilepsy and non-epileptic events. *Arch Dis Child* 2005;90:1219-1222.
2 Benbadis S. The differential diagnosis of epilepsy: a critical review. *Epilepsy Behav* 2009;15:15-21.
3 Hayes SM, Melin JD, Dupuis M, Murray S, Labiner DM. Assessing the true learning needs of health care professionals in epilepsy care. *Epilepsy Behav* 2007;11:434-441.

Activity Goal

To highlight the latest evidence for current and emerging treatments and translate guidelines into improved care of patients with epilepsy.

Learning Objectives

At the end of this CE activity, participants should be able to:

- Recognize the symptoms of epilepsy and list the components required to make an accurate diagnosis.
- Demonstrate improved expertise in the pharmacologic management of patients with epilepsy.
- Translate available guidelines for the treatment of epilepsy into clinical practice.

The following learning objectives pertain only to those requesting CNE credit:

- Recognize the symptoms of epilepsy.
- Identify available guidelines for the treatment of epilepsy.

Target Audience

Neurologists, epileptologists, other physicians, physician assistants, nurses, nurse practitioners, psychologists, pharmacists, social workers, certified case managers, and other healthcare professionals interested in the improvement of healthcare for patients with epilepsy.

CREDIT INFORMATION

CME Credit (Physicians)

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Accreditation Statement

Indiana University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation Statement

Indiana University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™* . Physicians should only claim credit commensurate with the extent of their participation in the activity.

Note to Physician Assistants: *AAPA accepts Category I credit from AOACCME, Prescribed credit from AAFP, and AMA Category I CME credit for the PRA from organizations accredited by ACCME*

CNE Credit (Nurses)

This continuing nursing education activity was approved by the New York State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

It has been assigned approval code 82LJZ9-10. 1.0 contact hours will be awarded upon successful completion.

CEP Credit (Psychologists)
CME Outfitters is approved by the American Psychological Association to sponsor continuing education for psychologists. CME Outfitters maintains responsibility for this program and its content. (1.0 CE credits)

NASW Credit (Social Workers)
This program was approved by the National Association of Social Workers (provider #886407722) for 1 continuing education contact hour.

CCMC Credit (Certified Case Managers)
This program has been approved for 1 hour by the Commission for Case Manager Certification (CCMC).

CPE Credit (Pharmacists)
CME Outfitters, LLC, is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. 1.0 contact hours (0.1 CEUs)
Universal Program Number: 376-999-10-006-H01-P

Activity Type: knowledge-based

All other clinicians will either receive a CME Attendance Certificate or may choose any of the types of CE credit being offered.

Financial Support
This activity is supported by an unrestricted educational grant from Pfizer Inc.

CREDIT REQUIREMENTS

Successful completion of this CE activity includes participating in the live activity, reviewing the course materials, and following the instructions below by March 24, 2011:

To complete your credit request form, activity evaluation, and post-test online, and print your certificate or statement of credit immediately (70% pass rate required), please visit www.neuroscienceCME.com and click on the Testing/Certification link under the Activities tab (requires free account activation). This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit www.neurosciencecme.com/technical.asp.

There is no fee for participation in this activity. The estimated time for completion is 60 minutes.
Questions? Please call **877.CME.PROS**.

FACULTY BIOS & DISCLOSURES

Cynthia L. Harden, MD
Dr. Harden joined the University of Miami in August 2008 and is Pending Rank Professor of Neurology at the University of Miami Miller School of Medicine. She is trained and certified in neurology and clinical neurophysiology. She is an internationally recognized expert in the treatment of seizure disorders, with an interest in issues for women with epilepsy, including pregnancy, neuroendocrine issues in epilepsy, new medical treatments for seizures, and psychiatric concerns for people with epilepsy. Dr. Miller recently led the committee to write American Academy of Neurology evidence-based guidelines for the management of women with epilepsy and pregnancy issues; these three articles were published in April 2009 with Dr. Harden as the first author. Dr. Harden has been PI or co-investigator on multiple NIH grants and multiple industry-sponsored, investigator-initiated clinical research projects.

Michael R. Sperling, MD
Professor Sperling is the Baldwin Keyes Professor of Neurology and Vice Chairman for Clinical Affairs in the Department of Neurology at Thomas Jefferson University in Philadelphia, PA. He is the Director of the Jefferson Comprehensive Epilepsy Center and the Clinical Neurophysiology Laboratory at Thomas Jefferson University Hospital. He has been published widely in both international and national medical journals including Epilepsia, Neurology, Journal of the American Medical Association, and Annals of Neurology, with more than 200 original papers, reviews, and book chapters, and over 200 abstracts. He has also published an EEG atlas and a textbook on the pharmacologic management of epilepsy. He has received grants from the National Institutes of Health and private industry for research in epilepsy, with a focus on the surgical treatment of epilepsy, mortality

in epilepsy, epilepsy genetics, and clinical neurophysiology. He lectures at many international and national meetings and has organized numerous conferences. Professor Sperling is an active member of many professional organisations including the American Epilepsy Society, American Clinical Neurophysiology Society, and the American Academy of Neurology, and is past-President of the American Clinical Neurophysiology Society and the Philadelphia Neurological Society. Professor Sperling is also an associate editor of Epilepsia and is a reviewer for numerous medical journals.

Vicenta Salanova, MD, FAAN (Content/Peer Reviewer)

Dr. Salanova is a Professor of Neurology at Indiana University School of Medicine, and Director of the Indiana University Comprehensive Epilepsy Program. Dr. Salanova earned her medical degree at the University of Madrid Medical School, and completed a fellowship in Epilepsy and Clinical Neurophysiology at the Cleveland Clinic Foundation.

For three years from 2002-2005, Dr. Salanova was named one of the Best Doctors in America. She is certified by the American Board of Psychiatry and Neurology. Dr. Salanova has published several peer-reviewed articles in journals such as the Annals of Neurology, Acta Neurologica Scandinavica, and Epilepsia. Her current research interests include refractory epilepsy, neurostimulators, and radiosurgical treatment of temporal lobe epilepsy.

Disclosure Declaration

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Note: While it offers CME credits, this activity is not intended to provide extensive training or certification in the field.

Dr. Harden has disclosed that she receives grants/research support from Forest Laboratories, Inc., GlaxoSmithKline, Pfizer Inc., and UCB Pharma. She has received honoraria from GlaxoSmithKline, Pfizer Inc., and UCB Pharma.

Professor Sperling has disclosed that he has received honoraria for speaking from GlaxoSmithKline, Pfizer Inc., and UCB Pharma. He has received honoraria for consulting from Dainippon Sumitomo Pharma Co., Ltd., and has received research support from H. Lundbeck A/S, Medtronic, Inc., Neuropace, Sepracor Inc., and UCB Pharma.

Dr. Salanova has no disclosures to report.

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Faculty of this CE activity may include discussions of products or devices that are not currently labeled for use by the FDA. The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

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Activity Slides

The slides that are presented in this activity are available for download and printout at the neuroscienceCME website: **www.neuroscienceCME.com.** Activity slides may also be obtained via fax or email by calling **877.CME.PROS**.

Abbreviation List

AED	Antiepileptic drug
AUC	Area under curve
AV	Atrioventricular
BE	Bioequivalence
BID	Twice daily
CBZ	Carbamazepine
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CoQ10	Coenzyme 10
CNS	Central nervous system
CPS	Complex partial seizures
CT	Computed tomography
EEG	Electroencephalography
EKG	Electrocardiography
FDA	Food & Drug Administration
FSIQ	Full scale intelligence quotient
GABA	Gamma-aminobutyric acid
ILAE	International League Against Epilepsy
IQ	Intelligence quotient
IRR	Incidence rate ratio
IS	Infantile spasms
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
LCM	Lacosamide
LTG	Lamotrigine
LVT	Levetiracetam
MCM	Major congenital malformations
MDI	Mental development index
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
NAAED	North American Antiepileptic Drug pregnancy registry
NIH	National Institutes of Health
OXC	Oxcarbazepine
PB	Phenobarbital
PET	Positron emission tomography
PHT	Phenytoin
PIQ	Performance intelligence quotient
PK	Pharmacokinetic
qd	Once a day
RFM	Rufinamide
SHARE	Support, Help and Resources for Epilepsy
SPECT	Single-photon emission computed tomography
SPS	Simple partial seizures
TPM	Topiramate
VGB	Vigabatrin
VIQ	Verbal intelligence quotient
VPA	Valproate
WBC	White blood cells
WWE	Women with epilepsy

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- ***Research Support:*** Forest Laboratories, Inc., GlaxoSmithKline, Pfizer Inc., UCB Pharma
- ***Honoraria:*** GlaxoSmithKline, Pfizer Inc., UCB Pharma

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Disclosures

- ***Speaker:*** GlaxoSmithKline, Pfizer Inc., UCB Pharma
- ***Consultant:*** Dainippon Sumitomo Pharma Co., Ltd.
- ***Research Support:*** H. Lundbeck A/S, Medtronic, Inc., Neuropace, Sepracor Inc., UCB Pharma

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any use not approved by the FDA) of products or devices.

Learning Objectives

- Recognize the symptoms of epilepsy and be able to list the components required to make an accurate diagnosis
- Demonstrate improved expertise in the pharmacologic management of patients with epilepsy
- Translate available guidelines for the treatment of epilepsy into clinical practice

Learning Objectives

Those applying for nursing credit should be able to:

- Recognize the symptoms of epilepsy
- Identify available guidelines for the treatment of epilepsy

The course guide for this activity includes slides, disclosures of faculty financial relationships, and biographical profiles.

For additional copies of these materials, please visit neuroscienceCME.com/440 or call 877.CME.PROS.

To receive CME/CE credits for this activity, participants must complete the post-test and evaluation online at neuroscienceCME.com/test

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Case Study

Fred, 80-Year-Old Man

Fred, 80-Year-Old Man

- History of partial seizures since age 66
- Wife states he stops what he was doing and may make sniffing noises, becomes unresponsive for about 1 minute
  - No warning or postictal state
  - No history of convulsions
- Gabapentin was first treatment begun 10 years ago (after 4 years of events)
- Had a car accident while driving 4 years ago and levetiracetam was prescribed
  - Levetiracetam made symptoms mild and briefer (same frequency)
  - Increased dose to 1250 mg BID

Fred, 80-Year-Old Man

- CT of head shows mild bifrontal atrophy
  - History of pacemaker placement 5 years ago
- EEG normal
- No risk factors for epilepsy
- Current meds
  - Warfarin sodium 7.5 mg for 6 days, and 5 mg for one day
  - Tamsulosin hydrochloride 0.4 mg per day
  - Folic acid 1 mg qd
  - Simvastatin 40 mg per day
  - Niacin 1000 mg
  - Trandolapril 5 mg per day
  - Docustate 100 mg BID
  - Co Q 10 every other day
  - Ezetimibe 10 mg
  - Levetiracetam 1250 mg BID

Fred, 80-Year-Old Man

- Levetiracetam increased to 1500 mg BID, but seizures continued
- Lamotrigine added
  - Patient felt dizzy, tired, and irritable
  - Could not tolerate 75 mg BID
  - Plasma level on 25 mg BID is 1.7 mcg/mL
- Lamotrigine stopped
- Lacosamide added and slowly increased to 100 mg BID with no seizures and occasional fatigue

Seizures and Epilepsy

- 10% of population has at least one seizure during lifetime[1]
  - Greatest risk in first year of life
  - Risk is reduced by half in childhood and adolescence
  - Risk increases after age 60
- Annual incidence in prospective Icelandic study[1]
  - First unprovoked seizures: 56.8 per 100,000
  - Single unprovoked seizure: 23.5 per 100,000
  - Epilepsy: 33.3 per 100,000
- In meta-analysis of 13 studies[2]
  - Recurrence risk for seizures after approx 2 years was 36% in prospective and 47% in retrospective studies

1. Olafsson E, et al. *Lancet Neurology* 2005;4:627-634.
2. Berg AT, et al. *Neurology* 1991;41:965-972.

Diagnosing Epilepsy and Seizures

- Diagnosis of seizures is not always simple
  - Variability of symptoms (e.g., lack of witness, patient may be entirely unaware of symptoms, odd behaviors, funny twitches, co-existing medical or psychiatric syndrome)
- Multiple conditions may mimic seizures
  - Psychogenic seizures, panic attacks
  - Cardiogenic and vasovagal syncope
  - Transient ischemic attacks, complicated migraine
  - Sleep disorders, movement disorders

Diagnosing Epilepsy and Seizures (cont.)

- Having a seizure does not necessarily lead to diagnosis of epilepsy—diagnosis presumably has therapeutic implications
  - ILAE criteria requires 2 seizures prior to establishing diagnosis
  - Criteria not always observed in practice when deciding to prescribe therapy

Accuracy of Diagnosis

- Diagnosis relies on accurate history, ideally eyewitness description of seizure
  - Reliability of witness is often doubtful
  - Even neurologists can disagree—NIH study of video analysis by epilepsy specialists showed high error rate
  - Misdiagnosis of 23% in UK population study[1] and 16% in hospital-based study[2]
    - Rate of error lower for neurologists—5.6%
    - Rate of error higher for nonspecialists—19.3%
- Rare for seizure to occur when in presence of physician
  - Requires accurate description by witness, skilled history by physician
  - Interrater reliability of physician history unknown
  - Witness reliability unknown

1. Scheepers B, et al. *Seizure* 1998;7:403-406.
2. Leach JP, et al. *Seizure* 2005;14:514-520.

Clinical Criteria to Diagnose Seizures

- Description of event should be consistent with seizure[1,2,3,4]
  - Usually positive phenomenon instead of negative phenomenon (exception: aphasia, rarely weakness)
  - Abrupt start, brief duration (seconds to few minutes), and clear cessation
  - Recurrent, stereotyped behaviors, perhaps transient postictal state
  - Description should be typical for seizures—ample literature descriptions of characteristic phenomena

See supplemental bibliography for full references.

Clinical Criteria to Diagnose Seizures (cont.)

- Presence of risk factors for seizures or epilepsy[1,2,3,4]
  - Transient disturbance known to provoke seizures: e.g., hypoglycemia, head trauma
  - Remote brain injury, developmental delay, cognitive impairment
  - Family history of epilepsy
  - Abnormal neurological examination
- Response to antiepileptic therapy does not confirm diagnosis[1,2,3,4]
  - Placebo, psychotropic, anti-movement disorder, and other effects

See supplemental bibliography for full references.

Suspicion of Alternate Diagnosis

- Event description might have features of other conditions
  - Antecedent lightheadedness with pallor and sweating suggest hypotension
  - Negative phenomena (e.g., paralysis) suggest ischemia
  - Prolonged symptoms with or without headache (e.g., 10-20 minutes) suggest migraine or ischemia
  - Start-stop-start movements, eyes closed, side-to-side head movement, antecedent headache, awareness of bilateral shaking, multiple seizure types suggest psychogenic etiology
  - Jerks may occur in hypoxia, different character

Suspicion of Alternate Diagnosis (cont.)

- History of non-neurologic condition that might cause paroxysmal symptoms
  - Psychiatric disorder, prior abuse
  - Cardiac rhythm disturbance
  - Sleep disorder
  - Movement disorder

Laboratory Tests

- May assist in confirming diagnosis
  - Mainly supportive of clinical impression
- EEG
  - Interictal spikes present in only 50-90% of patients (depends on method); presence doubles risk of recurrence after 1 seizure
  - Some normal people have abnormal EEGs
  - Incorrect interpretation—false negative and positive
  - Recording a seizure can prove diagnosis, but EEG may be negative in SPS or some frontal CPS
- MEG—not indicated for diagnosis
- Imaging
  - MRI or CT lesion supports increased risk for seizures
  - PET, SPECT: not indicated for diagnosis
- Laboratory tests
  - Elevated WBC, serum prolactin, and temperature immediately after seizure support diagnosis
  - Lack of these features does not militate against diagnosis

Conclusions

- No substitute for experience and judgement
  - Seizures tend to fit patterns
  - Diagnosis is pattern recognition
- Be prepared to question your diagnosis
- History is the key feature
  - Test results should help verify clinical impression, not provide diagnosis

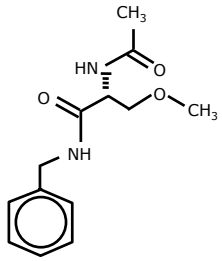
Anticonvulsants

- Carbamazepine
- Divalproex sodium
- Ethosuximide
- Gabapentin
- Lacosamide*
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Phenytoin sodium
- Pregabalin
- Rufinamide*
- Topiramate
- Valproic acid
- Vigabatrin*
- Zonisamide

* new agent

Lacosamide (LCM)

- FDA indications:
  - Indicated for adjunctive therapy for partial-onset seizures in patients ≥ 17 years
  - IV is indicated as short-term replacement when oral administration is not feasible in these patients
  - (R)-2-acetamido-N-benzyl-3-methoxypropanamide (IUPAC)



Drugs@FDA. FDA/Center for Drug Evaluation and Research.

LCM Dosing

- Twice daily: initial dose should be 50 mg twice daily (100 mg per day)
  - Increase at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day
  - Based on individual patient response and tolerability
- In clinical trials, the 600 mg daily dose was not more effective than the 400 mg daily dose, but had a substantially higher rate of adverse reactions

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LCM

- Mechanism: selectively enhances slow inactivation of voltage-gated sodium channels
- Metabolism: 40% metabolized by methylation by CYP 2C19; renally cleared, half-life 13 hours
- No pharmacokinetic interactions
  - Does not rule out the possibility of pharmacodynamic interactions, particularly among drugs that affect the heart conduction system
- Side effects: besides dizziness, which can be limiting
  - Produced a small, dose-related increase in mean PR interval
  - Should be used with caution in patients with known conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block, and sick sinus syndrome without pacemaker)
  - In these patients with conduction block, get EKG before using LCM and monitor

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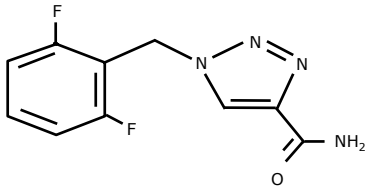
Rufinamide (RFM)

- FDA indication:
  - Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome for ages 4 years and above
  - Triazole derivative



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RFM Dosing

- Twice-daily dosing
  - Children four years and older with Lennox-Gastaut syndrome
    - Treatment should be initiated at a daily dose of approximately 10 mg/kg/day; increased by approximately 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day
  - Adults with Lennox-Gastaut syndrome
    - Treatment should be initiated at a daily dose of 400-800 mg/day, increased by 400-800 mg/day every 2 days until a maximum daily dose of 3200 mg/day

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RFM

- Mechanism of action unknown
- Possibly important is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel
- Metabolism-enzymatic hydrolysis not cytochrome P450 dependent
  - No known active metabolites
  - Half-life is approximately 6-10 hours
- Drug interactions: RFM is decreased by inducers
  - Increased by inhibitors (VPA)
- Side effects: somnolence, dizziness, ataxia
  - No warnings yet except suicide as for all AEDs
- Important safety information, contraindications
  - Patients with familial Short QT syndrome
  - Caution should be used when administering RFM with other drugs that shorten the QT interval

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Vigabatrin (VGB)

- Other FDA indications:
  - Infantile spasms (1 month to 2 years of age)
    - Monotherapy for pediatric patients with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss
  - Complex partial seizures
    - Adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
    - Not indicated as a first-line therapy agent for CPS

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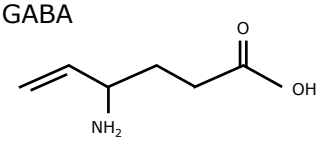
VGB

- Mechanism of action
  - Probably irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA
  - This action results in increased levels of CNS GABA



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VGB

- VGB causes permanent vision loss in infants, children, and adults
  - Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children is poorly characterized
  - For this reason, the data described below is primarily based on the adult experience:
    - In adults, VGB causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability
      - In some cases, VGB can also damage the central retina and may decrease visual acuity
    - Because of the risk of permanent vision loss, VGB is only available through SHARE, which is a special restricted distribution plan
      - Physicians must register with SHARE to begin prescribing VGB for their patients

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VGB Prescribing Info

- Review and sign Prescriber Enrollment and Agreement Form
  - Fax to SHARE Call Center at 1-877-742-1002
- By faxing the form to the SHARE Call Center, you will be registered to prescribe VGB
  - A confirmation will be sent from the SHARE Call Center, at which time you can begin prescribing VGB
- A Patient Starter Kit will be sent to you from the SHARE Call Center; additional kits will be provided by your Account Manager or can be requested from the SHARE Call Center at 1-888-45-SHARE

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Conclusions

- It's beneficial to have more options to help our patients
- Effectiveness (safety, tolerability, and efficacy) always plays out in the clinical arena and the clinical trials information is just a starting point!

Questions?

Type your question in the box at the bottom of this window and click the Submit button to send.

Cynthia L. Harden, MD

Michael R. Sperling, MD

Case Study

Nancy, 22-Year-Old Woman

Nancy, 22-Year-Old Woman

- A 22-year-old woman developed seizures at age 17
- Seizures begin with a feeling of dizziness followed by staring with unresponsiveness for 1-2 minutes
- Levetiracetam was first prescribed in doses up to 3000 mg/day without control; seizures occurred every 2-3 months
- At age 20, her physician prescribed branded topiramate at a dose of 150 mg per day and stopped levetiracetam, and she has had no seizures since then

Nancy, 22-Year-Old Woman

- Uses oral contraceptive medication (low dose estrogen/progesterone pill)
  - Plans to marry in 1 year, desires children soon
- Employed as secretary
- New issue:
  - Her insurance company has just informed her that since generic topiramate is now available, she has a "choice":
    - Switch to generic and pay $20 per 3-month supply
    - Continue branded topiramate—pay $180 per 3-month supply

Nancy, 22-Year-Old Woman
What Now?

- What should she do?
- Should she remain on branded agent or be switched to generic?
  - Does switching to generic pose risk?
  - If risk exists, how might it be mitigated?
- Should she switch to a different medication in view of her plans to start a family within a few years?
  - What is known about the teratogenicity of topiramate?
  - Are other medications preferable in this setting?

Risk of AEDs During Pregnancy

Study	Subgroup	Rate of MCM
Morrow J, et al. *J Neurol Neurosurg Psychiatry* 2006;77:193-198.	Untreated WWE Monotherapy with: VPA CBZ LTG All monotherapy All polytherapy	3.1% (8/227) 6.2% (44/758) 2.2% (20/900) 3.2% (21/647) 3.7% (91/2468) 6.0% (43/718)
Wide K, et al. *Acta Paediatr* 2004;93:174-176.	Monotherapy with: VPA CBZ	 9.7% (26/268) 4.0% (28/703)
Wyszynski DF, et al. *Neurology* 2005;64:961-965.	Monotherapy with: VPA All other AED monotherapy	 10.7% (16/149) 3.0% (31/1048)
Holmes LB, et al. *Epilepsia* 2004;45:1465.	Monotherapy with: PB Three other AEDs as monotherapy	 6.5% (5/77) 2.9% (23/796)

MCM = major congenital malformations; WWE = women with epilepsy; VPA = valproate; CBZ = carbamazepine; LTG = lamotrigine; AED = antiepileptic drug

Safety of AEDs During Pregnancy

AED Citation	% MCMs
PHT From Morrow J, et al. *J Neurol Neurosurg Psychiatry* 2006;77:193-198.	(n = 82) 3.7% (95% CI 1.3-10.2)
LVT From Hunt S, et al. *Neurology* 2006;67:1876-1879. From UCB AED Pregnancy Registry, 2-2009.	3/117 or 2.7% polytherapy 8/187 or 4.3% monotherapy
TPM Hunt S, et al. *Neurology* 2008;71:272-276.	3/70 or 4.8% monotherapy 95% CI 1.7% to 13.3%)
OXC From Novartis database reported by Montouris G. *Curr Med Res Opin* 2005;21:693-701.	6/248 or 2.4%

MCM = major congenital malformations; PHT = phenytoin; LVT = levetiracetam; TPM = topiramate; OXC = oxcarbazepine

Is Exposure to a Specific AED *in utero* Associated with Poor Cognitive Outcomes? From Practice Parameters

- VPA:[1,2,3]
  - Cognitive outcomes are reduced in children exposed to VPA during pregnancy
  - In all studies, risks for VPA were dose dependent and greater than non-exposed controls and children exposed to CBZ
  - Clinically important effect; a reduced verbal IQ of about 6-10 points below expected[2]

1. Adab N, et al. *Cochrane Database Syst Rev* 2004;(3):CD004848. Review.
2. Gaily E, et al. *Neurology* 2004;62:28-32.
3. Meador KJ, et al. *N Engl J Med* 2009;360:1597-1605.

Is Exposure to a Specific AED *in utero* Associated with Poor Cognitive Outcomes? From Practice Parameters

- CBZ:
  - CBZ does not increase poor cognitive outcomes compared to unexposed controls[1,2,3,4,5]
- PHT:
  - PHT poses an increased risk for poor cognitive outcomes compared to unexposed controls[4,5,6]
- PB:
  - One study with two cohorts shows reduced VIQ, PIQ, and FSIQ in adult men with PB exposure *in utero* compared to controls[7]

VIQ = verbal IQ; PIQ = performance IQ; FSIQ = full scale IQ; PB = phenobarbital
See supplemental bibliography for complete references.

Does AED Polytherapy Exposure During Pregnancy Pose an Increased Risk for Poor Cognitive Outcome Compared to Monotherapy? From Practice Parameters

- Three studies show that cognitive outcomes are reduced in children exposed to AED polytherapy compared to monotherapy[1,2,3]
  - Outcome assessments included IQ, VIQ, MDI

VIQ = verbal IQ; MDI = mental development index

1. Koch S, et al. *Epilepsia* 1999;40:1237-1243.
2. Gaily E, et al. *Neurology* 2004;62:28-32.
3. Lösche G, et al. *Acta Paediatr* 1994;83:961-966.

Conclusions

- Avoid VPA during pregnancy if possible either alone or as part of polytherapy
- Consider LTG, TPM, and LVT as AEDs to try instead for primary generalized epilepsies
- Polytherapy without the use of VPA in the regimen appears to add little increased risk of MCMs
  - Unknown regarding cognitive outcomes
- All other AEDs except perhaps PB appear to have lower risk of teratogenesis than VPA
  - Even their risk may be very slightly elevated from expected
  - The evidence for safety is best for CBZ and LTG so far

PB = phenobarbital

Conclusions (cont.)

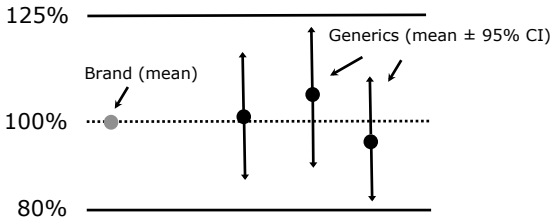
- CBZ is the easiest AED to manage during pregnancy with the least expected change in levels
  - With vigilant monitoring and dosage adjustment, seizure frequency can be maintained with other AEDs as well
- LTG would be a reasonable option, but levels may plummet during pregnancy
  - Dose adjustments are required
- Seizures are risky and should be avoided
  - If VPA is the only AED that controls seizures, the increased risk should be discussed including that MCMs do not occur in 90% of VPA-exposed babies
  - More difficult to comment on cognitive outcomes

Generic Drug Considerations

- Bioequivalence (BE) criteria[1]
  - The 90% confidence intervals of the geometric mean of the AUC and Cmax of the generic drug must fall within 80% to 125% of the reference drug (most drugs fall within 5%, but AEDs not known)[2]
- BE studies use healthy volunteers (number depends on PK variability)
  - Many patients take multiple medications that may affect drug absorption, metabolism, and clearance
  - No comparative data in children or elderly, who also take AEDs
- BE studies use a single-dose study in fasting and fed states
  - Single-dose BE studies not necessarily relevant to the chronic use of AEDs (repeated dosing)
- Generic products may differ in the manufacturing process, excipients used, and in final product appearance
  - Can lead to differences in drug disintegration, dissolution, and absorption rates
- BE is only tested between the generic product and reference brand
  - Use of multiple generic products could lead to substantial fluctuations in PK parameters and patient response

1. CDER 2003. http://www.fda.gov/cder/guidance/index.htm.
2. Abstract 1285. 2009 AAPS Annual Meeting and Exposition.

What Are FDA Rules Regarding Generics?



Q: How much does the mean of a generic differ from the mean of the brand?

A: Approx 5-7% (so swing between generics ≤ 10-14%)

Bialer M. *Epilepsia* 2007;48:1825-1832.

Implications of Brand to Generic Conversion in Epilepsy Patients

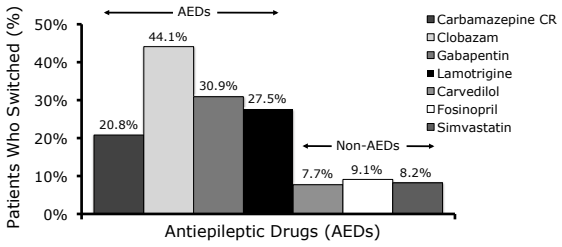
- Manufacturers do not need to demonstrate equivalence in side effects, efficacy, or safety to the reference brand
- Psychological issues
  - Patient anxiety may increase and lead to reporting of side effects
  - Changes in shape/color may lead to reduced adherence
    - Disruption in routine/habit of cognitively impaired patient
- Safety issues
  - Fluctuations in serum concentrations may lead to breakthrough seizures or loss of seizure control
  - Risk of injury (physical and psychological) from seizure occurrence
  - Patients near toxicity thresholds and those more susceptible to side effects may experience more adverse effects with serum concentration fluctuations
  - Many newer AEDs do not have a clear relationship between levels and seizure control or side effects, so there is no objective method to proactively assess this
- Legal issues
  - Seizure occurrence must be reported to department of motor vehicles
  - Loss of driving privileges may result in lost wages or employment

Generic Substitution of Topiramate

- Canadian study of topiramate substitution[1]
  - 948 patients observed during 1,105 person-years of brand use, 233 person-years of single-generic use, and 92 person-years of multiple-generic use
  - Multiple-generic use was associated with higher hospitalization rates (0.48 vs. 0.83 visits/person-year; incidence rate ratio (IRR) 1.65) and longer hospital stays (2.6 vs. 3.9 days/person-year; IRR 1.43)
  - The effect was less pronounced in single-generic use (hospitalization: IRR 1.08; length of stay: IRR 1.12)
  - The risk of head injury or fracture was nearly three times higher (hazard ratio 2.84, 95% CI 1.24–6.48) following a generic-to-generic switch compared to brand use
  - Total annualized healthcare cost per patient was higher in the multiple-generic than brand periods by Can$1,716 (cost ratio 1.21, p = .042)

1. Duh MS, et al. *Neurology* 2009;72:2122-2129.

Generic Substitution of Lamotrigine *Switchback to Brand (%)*



- Of 671 patients treated with branded lamotrigine:
  - 187 patients (27.9%) switched to a generic; 51 of these patients (27.5%) switched back to the branded medication
  - Rates of switchback were from 20.8% to 44.1% for various AEDs and from 7.7% to 9.1% for non-AEDs

LeLorier J, et al. *Neurology* 2008;70:2179-2186.

Generic Substitution of Lamotrigine

- Relative to the branded lamotrigine use period, generic lamotrigine use period was associated with:
- A 5.1% increase in mean daily dose of lamotrigine (239.1 vs. 251.4 mg; $p = .0149$)
- A higher number of dispensations for other AEDs (20.4 vs. 23.9 dispensations per person-year; $p < .001$) as well as non-AED drugs (26.4 vs. 32.8 dispensations per person-year; $p < .0001$)
- A higher utilization rate of medical services (8.7 vs. 9.8 visits per person-year; $p < .0001$)
- A longer hospital length of stay (3.29 days vs. 4.86 days per person-year; $p < .0001$)

LeLorier J, et al. *Neurology* 2008;70:2179-2186.

Approach for Generic AEDs

- Initiating therapy: consider treatment with generic AED
  - Because of bioequivalence variability between generic products, advise use of same generic product at each refill
- Not fully controlled: generic substitution could be tried in patients who are not controlled on current AED regimen
  - Because of bioequivalence variability between generic products, advise use of same generic product at each refill
  - Observe closely for side effects or worsened seizure control—requires close medical supervision
- Seizure-free: avoid generic substitution
  - Matters can only get worse
  - Some insurance plans make this prohibitively expensive

Questions?

Type your question in the box at the bottom of this window and click the Submit button to send.

Cynthia L. Harden, MD

Michael R. Sperling, MD

Resources

- International League Against Epilepsy (ILAE) Treatment Guidelines
  - http://www.ilae-epilepsy.org/Visitors/Centre/AEDGuidelines.cfm
  - http://www.ilae-epilepsy.org/Visitors/Centre/Guidelines.cfm
- Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations (CDER/FDA)
  - http://ww.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf
  - http://www.fda.gov/cder/guidance/index.htm
- Practice Guidelines Pertaining to Pregnancy and Women with Epilepsy
  - Harden CL, et al. *Neurology* 2009;73;126-132 http://www.neurology.org/cgi/rapidpdf/WNL.0b013e3181a6b2f8v1.pdf
  - Harden CL, et al. *Neurology* 2009;73;142-149 http://www.neurology.org/cgi/reprint/73/2/142
- NAAED Pregnancy Registry
  - http:/www.aedpregnancyregistry.org
- UCB AED Pregnancy Registry
  - 1-888-537-7734 (1-888-KEP-PREG)

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Slide: Clinical Criteria to Diagnose Seizures

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