December 4 - 8 ■ Philadelphia, PA
69TH ANNUAL MEETING

Epilepsy Therapy Symposium
What You Need to Know to Get Your Patients Into the 65% Group

Symposium Co-Chairs:

Cynthia Harden, M.D.

and

Jerry Shih, M.D.

Saturday, December 5, 2015
Convention Center – Grand Ballroom AB

2:15 – 5:00 p.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
This symposium will guide the attendee in managing epilepsy patients from initial diagnosis to consideration of respective epilepsy surgery. Guidelines will be presented providing best practice for initiating anti-seizure drug therapy. Attendees will learn ways to recognize and manage drug "failures" that are not due to lack of drug efficacy. Updated information on best practices for rational polypharmacy to obtain the best patient outcomes will be presented. Newer nonpharmacologic treatments for patients who continue to have seizures despite adequate trials of anti-seizure medications will also be presented. The concept of anti-epileptic versus antiepileptogenic therapy for seizures will be discussed in a practical, clinically-based approach.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Manage new onset epilepsy utilizing evidence based practices
- Counsel patients and families regarding appropriate nonpharmacologic treatments
- Participate in counseling patients families about the importance of medication adherence to ensure maximum treatment efficacy
- Recognize risk factors for non-adherence to medication recommendations and counsels patients regarding adherence

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background in the specialty is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Agenda
Co-Chairs: Cynthia Harden, M.D. and Jerry Shih, M.D.

Introduction
Jerry Shih, M.D.

Treatment Strategies for Newly Diagnosed Epilepsy
Emilio Perucca, M.D., Ph.D.

When is “Drug Failure” Not a Drug Failure
Patrick Kwan, M.D., Ph.D.

Rational Polypharmacy – What Is the Evidence?
Josiane LaJoie, M.D.

Update on Nonpharmacologic Treatments
Christopher Skidmore, M.D.

Disease modifying Therapies
Current Status
Andrew Cole, M.D.

Conclusion
Cynthia Harden, M.D.

Education Credit
2.5 CME Credits

Nurses may claim up to 2.5 contact hours for this session.

Nurse Practitioners may claim 2.5 hours of pharmacology for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.5 contact hours (0.25 CEUs). UAN 0077-9999-15-031-L01-P. Initial Release Date: 12/5/2015.

The American Board of Psychiatry and Neurology has reviewed the What You Need to Know to Get Your Patient into the 65% Group Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Commercial Support Acknowledgement
Supported in part by educational grants from Eisai Inc., UCB, Inc., and Supernus Pharmaceuticals, Inc.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Cynthia Harden, M.D. (Co-Chair)
Cynthia L. Harden, MD received her medical degree at the University of Wisconsin in Madison. She trained in internal medicine at St. Luke's Hospital and neurology at Mount Sinai Hospital both in New York City, and in clinical neurophysiology at Albert Einstein College of Medicine in the Bronx. She has enjoyed a long career of carrying out original research, teaching and caring for patients, with publications in the subdisciplines of neuroendocrine aspects of epilepsy and psychiatric issues in persons with epilepsy. She served most of her career at the Weill Cornell College of Medicine in New York where she became Professor of Neurology. She is currently Director of Epilepsy Services for the Mount Sinai Health System in New York City.

Dr. Harden discloses receiving support for Royalties from Wiley, Up-to-date; as Contracted Research from NINDS (sponsored research.)

Jerry Shih, M.D. (Co-Chair)
Dr. Shih received his bachelor's degree from the Johns Hopkins University in 1980. He received his medical degree from the University of California, Los Angeles School of Medicine, and completed neurology residency and epilepsy/clinical neurophysiology fellowship at UCLA. Dr. Shih was Director of the Epilepsy Program, Associate Professor of Neurology, and Vice-Chair of Neurology at the University of New Mexico, School of Medicine. He is currently Director of the

Comprehensive Epilepsy Program at Mayo Clinic Florida, and Associate Professor of Neurology at Mayo College of Medicine. His early research was on the use of MEG in the evaluation of epilepsy. His current research is utilizing brain-computer interfaces to control external d

Dr. Shih discloses receiving support for Contract Research from UCB, Inc.; for Other Service from Board Member of NAEC (without compensation).

Andrew Cole, M.D.
Andrew J. Cole, MD, FRCP(C), is Professor of Neurology at Harvard Medical School and Director of the MGH Epilepsy Service and Chief of the Division of Clinical Neurophysiology Laboratory at Massachusetts General Hospital in Boston. Dr. Cole also directs Epilepsy and Clinical Neurophysiology Fellowship Program at MGH. Dr. Cole graduated magna cum laude from Dartmouth College in Hanover, New Hampshire, and obtained his medical degree from Dartmouth Medical School. He completed an internship in internal medicine at Case Western Reserve University in Cleveland, Ohio, and a residency and chief residency in neurology at the Montreal Neurological Institute, McGill University, Montreal, Quebec.

Dr. Cole discloses receiving support as Consulting Fee from Sage Therapeutics, Consulting Precsis AG Consulting; as Ownership Sage Therapeutics, Precisis Consulting

Patrick Kwan, M.D., Ph.D.
Patrick Kwan is Professor of Neurology at the University of Melbourne, and Head of Epilepsy at the Royal Melbourne Hospital, Melbourne, Australia. His research interests include the outcomes, pharmacology, genomics, pharmacogenetics, and mechanisms of drug of resistance in epilepsy. He serves as Associate Editor of Epilepsy Research, and is editorial board member of CNS Drugs, Epilepsy & Behavior, Epileptic Disorders, and Seizures. He is currently Chair of the ILAE Commission of Medical Therapies.

Dr. Kwan discloses receiving support as Consulting from Eisai, UCB Pharma; as Speakers Bureau from Eisai, Novartis, UCB Pharma, GSK; as Contracted Research from UCB Pharma, GSK, Eisai.

Josiane Lajoie, M.D.
Dr. Josiane LaJoie is an Associate Professor of Neurology and Pediatrics at NYU Langone Medical Center. She completed her pediatric training at The New York Hospital of the New York Presbyterian Hospital System. She completed a Pediatric Neurology Residency and a Clinical Neurophysiology Fellowship at the Albert Einstein College of Medicine. For several years she has served on the Professional Advisory Board for the Epilepsy Foundation of America and currently serves on the professional advisory board of the Epilepsy Foundation of Metropolitan of New York and Long Island. She is board certified in General Pediatrics, Neurology with special qualification in pediatric neurology and Clinical Neurophysiology.

Dr. Lajoie has indicated she has no financial relationships with commercial interests to disclose.

Dr. Lajoie does intend to discuss unlabeled/unapproved drugs or products – Stiripentol.

Emilio Perucca, M.D., Ph.D.
Emilio Perucca obtained a M.D. degree at the University of Pavia in 1975 and a Ph.D. Diploma at the University of London in 1980. He trained as a neurologist and clinical pharmacologist at the National Hospital for Nervous Diseases, London. He is currently Professor at the University of Pavia and Director of the Clinical Trial Centre at the C. Mondino National Neurological Institute in Pavia. He is the current President of ILAE. He is a member of the editorial/advisory board of several journals, including

Epilepsia, Epileptic Disorders, Epilepsy Research, Seizure, Lancet Neurology, and CNS Drugs. His special interests are drug treatment and outcome assessment in epilepsy.

Dr. Perucca discloses receiving support for Royalties from Wiley (as co-editor of a textbook on the treatment of epilepsy), Elsevier, for authorship of article "Epilepsy: New Advances' published in The lancet (2014); for Consulting Fee from GW Pharma, Biopharm Solutions, Takeda; for Contract Research from UCB Pharma, investigator for a non-product oriented epilepsy study - indirect payment made to my Institution; for Honoraria from UCB Pharma, Sun Pharma; for Other Services from ILAE, President (no compensation), LICE Foundation (President), Italian League against Epiepsy (no compensation), Epilepsy Alliance Europe, Director (no compensation).

Dr. Perucca does intend to discuss unlabeled/unapproved drugs or products – Potentially all AEDs.

Christopher Skidmore, M.D.
Dr. Christopher T. Skidmore is an Assistant Professor of Neurology at the Sidney Kimmel College of Medicine at Thomas Jefferson University and a member of the Jefferson Comprehensive Epilepsy Center. In addition to his work in epilepsy, he serves as the neurology residency program director. He is a graduate of Saint Louis University School of Medicine and completed his neurology and epilepsy training at the Cleveland Clinic Foundation in Cleveland, OH.

Dr. Skidmore discloses receiving support for Contract Research from Neuropace, Inc as the site PI; for Honoraria from PVI / Penn State CME: I give CME sponsored grand rounds on epilepsy treatment and new AEDs for which I receive an honorarium; for Other Service from Board Member, Epilepsy Foundation of Eastern PA and Chair of the Professional Advisory Board.

CME Reviewer
Rohit Das, M.D.
Dr. Das discloses receiving support for Consulting from Upsher-Smith; as Honoraria from National Board of Medical Examiners (USMLE).

Kinshuk Sahaya, M.D.
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Neurology Residency Program Director
University of Arkansas for Medical Sciences, Little Rock, AR

Dr. Sahaya discloses receiving support for Honoraria from Reviews for Practical Reviews in Neurology by Oakstone Publishing.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS
Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

CLAIMING CREDIT:

PHYSICIANS

Physicians can claim CME credit online at **https://cme.experientevent.com/AES151/**

This Link is NOT Mobile-friendly! You must access it from a laptop, desktop or tablet.

How to Claim CME Credit

To claim CME credits online, please follow the on-screen instructions at the above url. Log in using your last name and zip code, OR your last name and country if you're not from the United States. All CME credits must be claimed **by February 26, 2106**.

Questions?

Contact Experient Customer Service at: 800-974-9769 or **AES@experient-inc.com**

NURSING & PHARMACY

PLEASE NOTE: Providing your NABP e-profile # is required.

The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER

Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

What You Need to Know to Get Your Patient into the 65% Group!

Co-chairs:

Jerry J. Shih, MD Mayo Clinic, Florida, USA

Cynthia Harden, MD Mount Sinai Health System New York, USA

December 5, 2015

American Epilepsy Society 69th Annual Meeting December 4 - 8, 2015 Philadelphia, PA

Disclosure

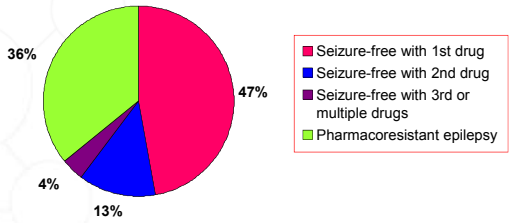
NSF	Research Grant
Eisai	Research Grant
UCB	Research Grant; Advisory Board
Visualase, Inc	Research Grant
Upsher-Smith Labs	Advisory Board

Learning Objectives

- Learn the current best practices for initiating anti-seizure drug therapy
- Recognize and manage drug "failures" not due to lack of drug efficacy
- Learn best practices for rational polytherapy
- Learn the nonpharmacologic treatments for epilepsy
- Understand the concept of anti-seizure versus anti-epileptogenic drug therapy

Response to Antiseizure Medication

Previously Untreated Epilepsy Patients (n=470)



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.

Program Overview

Introduction and Pre-test	Jerry Shih
Treatments for Newly Diagnosed Epilepsy	Emilio Perucca
When is "Drug Failure" not a Drug Failure	Patrick Kwan
Rational Polypharmacy	Josiane LaJoie
Update on Nonpharmacologic Treatments	Christopher Skidmore
Disease Modifying Therapy – Current Status	Andrew Cole
Conclusion and Post-test	Cynthia Harden

- ** Off-label uses of epilepsy Rx may be discussed **

Clinical Case

BH is a 22 year-old male presenting to outpatient clinic with a history of a generalized convulsion last week. Patient's girlfriend reported that he suddenly stopped talking and stared blankly. He exhibited repetitive lip licking movements, and then turned his head and eyes tonically to the right before stiffening all extremities and shaking for 30 seconds. Girlfriend reports a similar episode of behavioral arrest and confusion without convulsion two weeks before.

Clinical Case

Patient has a history of alcohol intoxication, and was involved in a car accident 6 months ago which resulted in loss of consciousness and a 3-day hospitalization. Brain MRI shows subtle left hippocampal volume loss without T2/FLAIR signal changes. EEG shows left temporal spike and sharp wave complexes.

Clinical Case

1. What is the best initial treatment for him?
2. What are possible causes of him continuing to have seizures after treatment
3. If anti-seizure drug monotherapy is not effective in controlling seizures, are there drug combinations that may improve seizure control?
4. Besides resective epilepsy surgery, are there effective non-drug treatment alternatives for his seizures?
5. What current treatment options can modify the epileptogenic network in this individual?

ARS Question #1

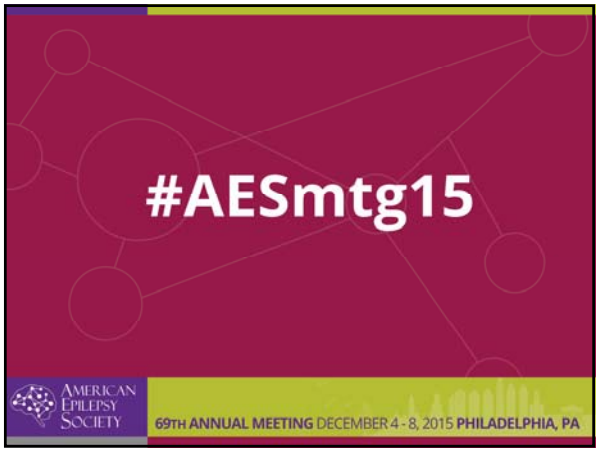
Which of the following statements is true?

1. Carbamazepine, lamotrigine, levetiracetam and gabapentin have similar effectiveness in newly diagnosed focal epilepsy
2. Evidence favors lamotrigine for females with childhood absence epilepsy
3. Valproate has unsurpassed efficacy in generalized epilepsies, but risks related to childbearing potential are a major concern
4. Rational antiseizure drug selection includes the concept of additive effects such as using pregabalin and gabapentin in combination

ARS Question #2

Which of the following statements is true?

1. "Pseudoresistance" refers to the concept of patients under-reporting good seizure control
2. A substantial proportion of patients (~33%) with seemingly uncontrolled epilepsy could become seizure free with further AED adjustment
3. In clinical trials, approximately half of patients starting the ketogenic diet, the modified Atkins diet, or the low glycemic index treatment have a >50% reduction of seizures
4. Levetiracetam and zonisamide have been shown in animal studies and human clinical trials to have anti-epileptogenic properties



Treatment Strategies for Newly Diagnosed Epilepsy

Emilio Perucca, MD

Clinical Trial Center, C. Mondino National Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Italy

December 5, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

The presenter has received grants, royalties and/or speaker/consultancy fees from:

- Biopharma Solutions
- Elsevier
- GW Pharma
- Sun Pharma
- Takeda
- UCB Pharma
- Wiley

Learning Objectives

- To be able to select the most appropriate initial treatment for patients with newly diagnosed epilepsy, based on best available evidence
- To be able to identify situations where treatment should be withheld
- To be able to optimize drug dosage in order to achieve the best benefit to risk ratio

Impact on Clinical Care and Practice

- Most patients who achieve freedom do so on the initially prescribed antiepileptic drug
  - Being able to select the most appropriate treatment is critical for long-term seizure outcome
- Personalizing drug choice and dosing scheme is essential to ensure maximum patient's benefit
  - Being able to tailor treatment to the characteristics of the individual is the key prerequisite to obtain a good therapeutic response without disabling adverse effects

Outline

- When should treatment be started?
- Which drug?
- Which dose?

Outline

- When should treatment be started?
- Which drug?
- Which dose?

ILAE OFFICIAL REPORT

Epilepsia, 55(4):475–482, 2014

A practical clinical definition of epilepsy

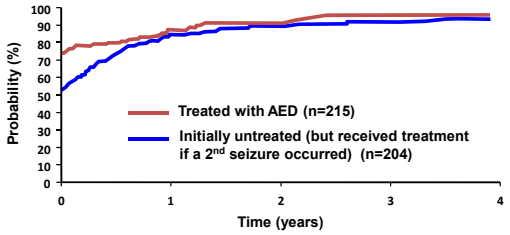
*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjorn Tomson, ####Masako Watanabe, and *****Samuel Wiebe

Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked seizures occurring ≥24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures over the next 10 years similar to the general recurrence risk (≥60%) after two unprovoked seizures
- Diagnosis of an epilepsy syndrome

Delayed Treatment Does Not Reduce Long-term Probability of Seizure Freedom

Probability of achieving1-year seizure freedom (FIRST trial)



FIRST = First Seizure Trial Group
AED = antiepileptic drug

Adapted from Musicco *et al. Neurology* 1997;49:991-8

Outline

- When should treatment be started?
- Which drug?
- Which dose?

Which Drug for Initial Therapy?

- Consider the properties of each individual drug, based on available evidence
- Consider their expected influence on probability of seizure control and well being
- Choose the drug whose properties provide the best match for the patient's needs

Which is the Best AED for my Patient? Properties to be Considered

- Spectrum of efficacy (seizure types and syndromes)
- Magnitude of efficacy
- Adverse effect profile (including teratogenicity)
- Impact on co-morbidities
- Drug interactions (and mechanisms of action)
- Ease of use
- Cost

Efficacy Spectrum of Available AEDs

Most seizures types/syndromes	Focal seizures and epilepsies*	Absence only
Valproic acid	Carbamazepine	Ethosuximide
Benzodiazepines	Phenytoin	
Phenobarbital°	Oxcarbazepine	
Primidone°	Pregabalin	
Levetiracetam	Gabapentin	
Lamotrigine°	Lacosamide	
Topiramate	Eslicarbazepine acetate	
Zonisamide	Tiagabine	
Rufinamide	Perampanel	
Felbamate	Vigabatrin	
	Retigabine	

* Some of these AEDs may also protect against primarily generalized tonic-clonic seizures. Most can exacerbate myoclonic / absence seizures. Vigabatrin is effective in infantile spasms

° Phenobarbital and primidone are not effective against absences. Lamotrigine may aggravate severe myoclonic epilepsy of infancy.

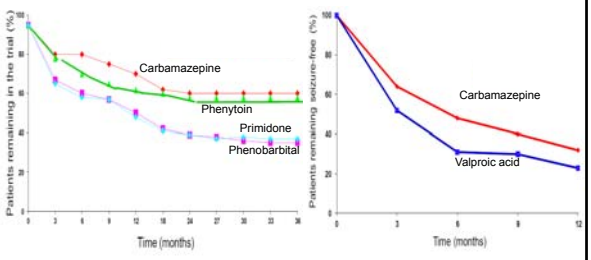
Modified from Perucca, *Epilepsia* 2005; 46 (suppl 4);31-7, Efficacy spectrum illustrated in this slide may not reflect U.S. prescribing information

AEDs Approved for Initial Monotherapy of Epilepsy in the U.S. and/or Europe

- Carbamazepine
- Clonazepam
- Gabapentin*
- Lacosamide*
- Lamotrigine*
- Levetiracetam*
- Oxcarbazepine
- Primidone
- Phenobarbital
- Phenytoin
- Topiramate
- Valproic acid
- Zonisamide*

* Not approved by the FDA for initial monotherapy
* Monotherapy indication not approved in Europe

Comparative Effectiveness/Efficacy of Older Generation AEDs in Patients with Focal Seizures



Mattson *et al. N Engl J Med* 1985;**313**:145–51

Mattson *et al. N Engl J Med* 1985;**313**:145–51

Comparative Efficacy of Newer and Older AEDs in Patients with Newly Diagnosed Focal Epilepsy

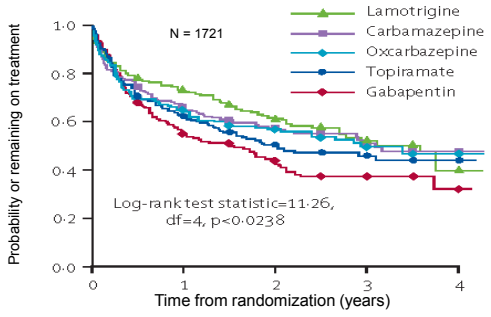
Systematic review of RCTs in newly diagnosed epilepsy – mostly patients with focal seizures

- Oxcarbazepine *vs* carbamazepine, valproate or phenytoin
- Lamotrigine vs carbamazepine, valproate or phenytoin
- Gabapentin vs carbamazepine
- Topiramate vs carbamazepine or valproate
- Levetiracetam vs carbamazepine
- Vigabatrin vs carbamazepine
- Zonisamide vs carbamazepine

Newer AEDs were not more efficacious than older drugs (gabapentin and vigabatrin being probably less efficacious)

Glauser et al, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2013;54:551-63.

Comparative Effectiveness of Gabapentin, Lamotrigine, Topiramate and Carbamazepine in Newly Diagnosed (mostly) Focal Seizures (SANAD A)



Lamotrigine and gabapentin are not FDA approved for initial monotherapy

Marson et al. *The Lancet* 2007;369;1000-15/1016-29

Quality of Randomized Trials in New Onset Epilepsy

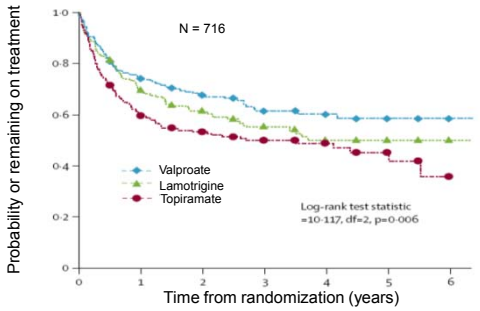
Rating by ILAE Criteria (Epilepsia 2013; 54:551-563)

Seizure type	N. of studies	Class I	Class II	Class III
Focal, adults	39	4	1	34
Focal, children	20	1	0	19
Focal, elderly	5	1	1	3
GTCS, adults	29	0	0	29
GTCS, children	14	0	0	14
Absence, children	7	1	0	6
BECTS	3	0	0	3
JME	1	0	0	1

BECTS = benign epilepsy with centrotemporal spikes; GTCS = generalized tonic-clonic seizures; JME = juvenile myoclonic epilepsy)

Glauser et al, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2013;54:551-63.

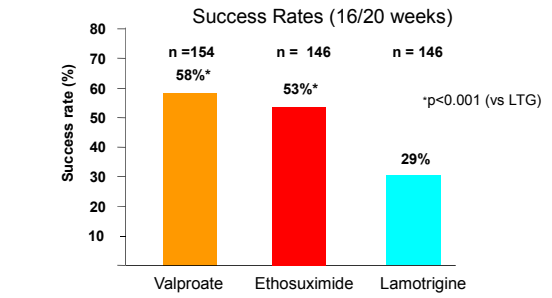
Comparative Trial of VPA vs LTG vs TPM in Newly Diagnosed (mostly) Generalised or Unclassified Epilepsy (SANAD B)



Lamotrigine is not FDA approved for initial monotherapy

Marson et al. *The Lancet* 2007;369;1000-15/1016-29

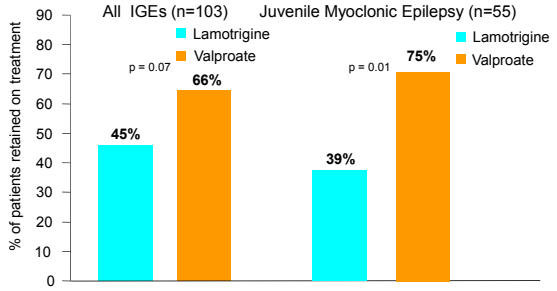
Lamotrigine vs Ethosuximide vs Valproic Acid in Newly Diagnosed Childhood Absence Epilepsy



Lamotrigine is not FDA approved for initial monotherapy

Glauser et al, *New Engl J Med* 2010; 362:790-9

Valproate vs Lamotrigine in Genetic (Idiopathic) Generalized Epilepsies: 1-Year Remission Rates on Initial Treatment



Lamotrigine is not FDA approved for initial monotherapy

Mohanraj and Brodie, *Acta Neurol Scand* 2007; 115:204-8

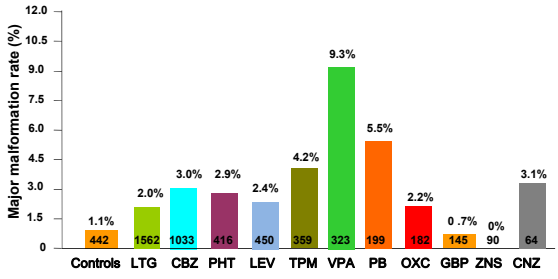
Which AED Shows the Best Efficacy / Effectiveness? Summary of the Evidence

- Carbamazepine, phenytoin, oxcarbazepine, lamotrigine, levetiracetam and zonisamide have similar effectiveness in newly diagnosed focal epilepsy
- Evidence favors ethosuximide for childhood absence epilepsy
- Valproate has unsurpassed efficacy in generalized epilepsies, but risks related to childbearing potential are a major concern
- Rational AED selection must consider other factors beyond efficacy

Beyond Efficacy: Other Factors Affecting Drug Selection, and Concerns for Special Groups

- Genotype and history of ADRs
  - avoid CBZ in HLA-B 15:02 and HLA-A 31:01 allele carriers
  - caution when using aromatic AEDs in individuals with a history of serious hypersensitivity to drugs
- Age and gender
  - age and gender are risk factors for some adverse AED reactions
- Comorbidities
  - AEDs may impact favorably or adversely on specific comorbidities
- Comedications
  - Avoid enzyme inducing AEDs in patients at risk for serious adverse interactions

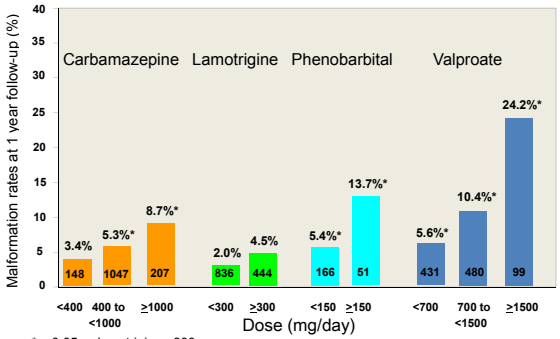
Major Malformation Rates in Monotherapy Exposures: North American Registry Data



CBZ = carbamazepine; CNZ = clonazepam; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin, TPM = topiramate; VPA = valproate; ZNS = zonisamide

Hernandez Diaz et al, *Neurology 2012;78:1692-9*

Major Malformations Rates in Offspring Exposed Prenatally to 4 Major AEDs: EURAP Registry Data



*p<0.05 vs lamotrigine <300mg

Tomson et al., *Lancet Neurol*, 2011;10:609-17

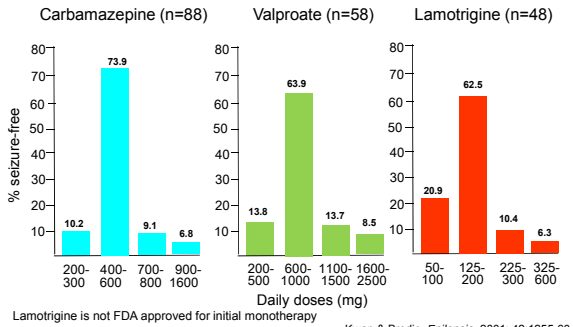
Outline

- When should treatment be started?
- Which drug?
- Which dose?

Critical Decisions on Dosing Strategies

- Which titration rate?
  - need for rapid therapeutic action vs risk of adverse effects
- Which initial target dose?
  - maximize early seizure control vs risk of using a dose higher than needed
- In non-responders, go up to highest tolerated dose?
  - risk vs benefit of going above predefined dose limits
  - role of serum drug level monitoring

A Review of Outcomes on the First Prescribed AED Doses at Which Seizure Freedom Was Achieved

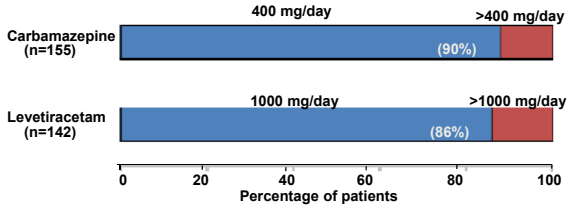


Lamotrigine is not FDA approved for initial monotherapy

Kwan & Brodie, *Epilepsia* 2001; 42:1255-60

Levetiracetam vs Carbamazepine-CR in Newly Diagnosed Focal Epilepsy

Distribution of Dosages in Patients Achieving 1-Year Remission

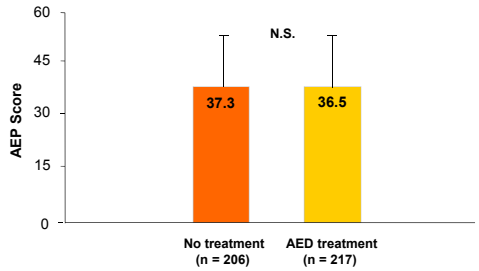


Levetiracetam is not FDA approved for initial monotherapy

Brodie et al. *Neurology* 2007; 68: 402-8

Using Low to Moderate AED Doses Prevent the Onset of Adverse Effects

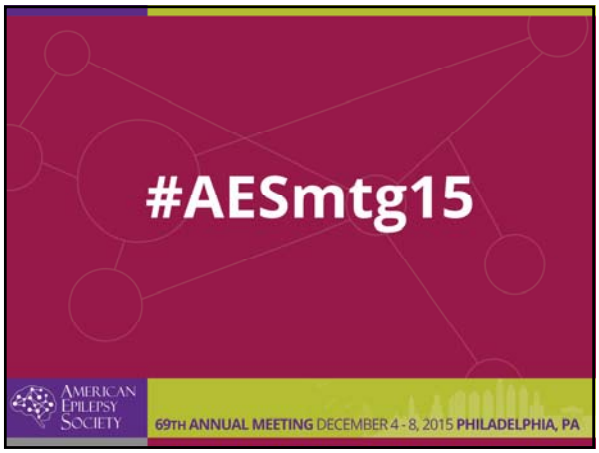
Toxicity (AEP) Scores from Two Large Prospective Studies (US and UK)



Perucca P et al. *Neurology* 2011;76:276-9.

Conclusions

- Treatment strategies in newly diagnosed epilepsy require balancing expected benefits vs risk in the individual
- There is suboptimal evidence to guide AED selection, particularly for generalized epilepsies
- Efficacy is only one of many factors guiding treatment selection
- Individualizing dose is as important as choosing the right drug


#AESmtg15
American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

When is "Drug Failure" Not a Drug Failure?

Patrick Kwan, MD, PhD
The University of Melbourne,
Royal Melbourne Hospital, Melbourne, Australia

The Royal Melbourne Hospital
MELBOURNE BRAIN CENTRE at The Royal Melbourne Hospital
THE UNIVERSITY OF MELBOURNE

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

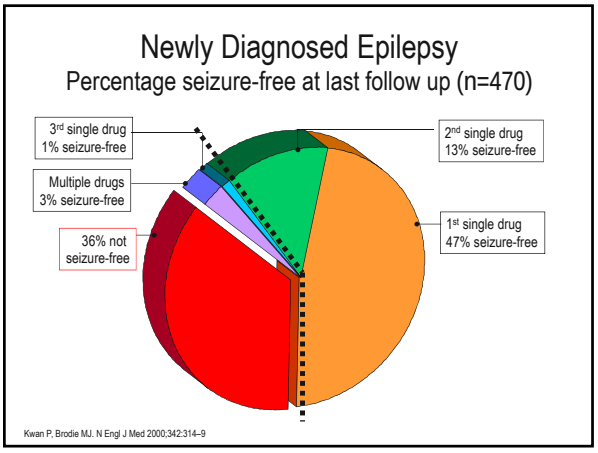
Eisai	Consultancy
Novartis	Consultancy
UCB Pharma	Sponsored research

Learning Objectives

- Understanding treatment outcomes in epilepsy
- Recognition of drug resistant epilepsy
- Recognition and management of drug failures not due to drug efficacy

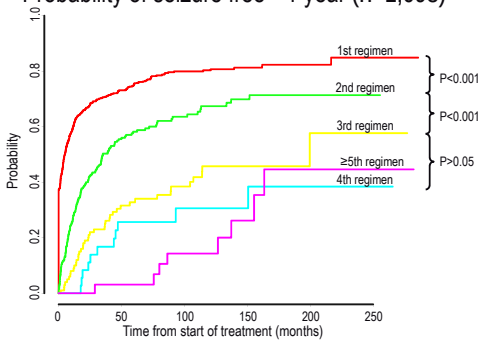
Impact on Clinical Care and Practice

- Developing a staged approach to epilepsy treatment
- When to consider non-drug therapies
- When to refer patients for specialist assessment
- Understanding the important of appropriate use of medications



Newly Diagnosed Epilepsy

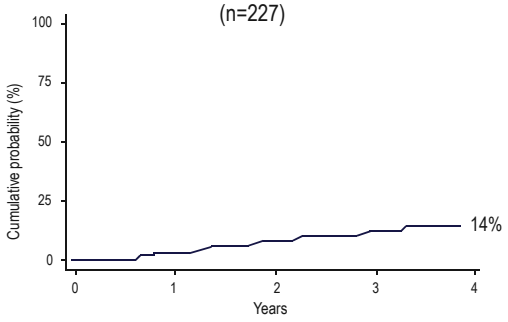
Probability of seizure free ≥1 year (n=1,098)



Brodie, Barry, Bamagous, Norrie, Kwan. Neurology 2012;78:1548–54

Chronic Epilepsy Failed ≥ 2 AEDs

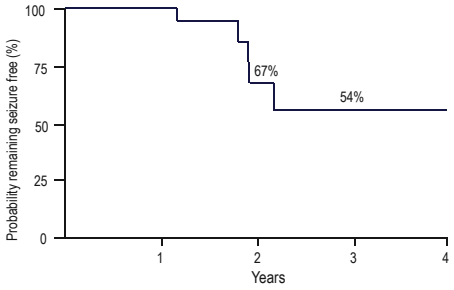
Probability seizure free with continued medical treatment (n=227)



Data from Callaghan et al. (2007)

Chronic Epilepsy Failed ≥ 2 AEDs

Relapse after seizure free for 1 year (20 of 187 patients treated medically)



Data from Choi et al. (2008)

Epilepsia
The Journal of the International League Against Epilepsy
Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

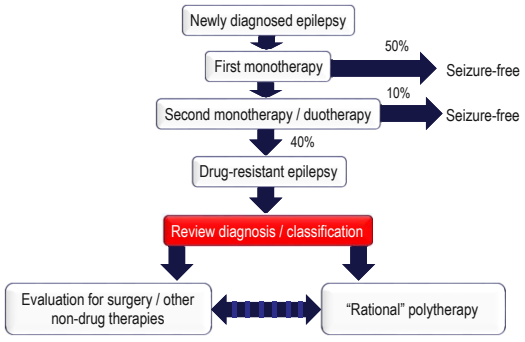
Failure of adequate trials of two (or more) tolerated and appropriately chosen and used antiepileptic drugs to achieve sustained seizure freedom

Newly Diagnosed Epilepsy

Slide not available

Chen, Brodie, Liew, Kwan. International Epilepsy Congress, Istanbul, Sep 2015

Treatment of epilepsy: an algorithmic approach



Modified from Kwan, Schachter, Brodie. N Engl J Med 2011;365:919–26

Ruling Out "Pseudoresistance"

Table 1. **Some Reasons for Pseudoresistance to Antiepileptic Drug Therapy.**

Reason	Examples
Wrong diagnosis	Syncope, cardiac arrhythmia, or other conditions; psychogenic nonepileptic seizures
Wrong drug (or drugs)	Inappropriate for seizure type; pharmacokinetic or pharmacodynamic interactions
Wrong dose	Too low (overreliance on "therapeutic" blood levels); side effects preventing drug increase
Lifestyle issues	Poor compliance with medication; alcohol or drug abuse

Perucca E. CNS Drugs1998;10:171-9
Kwan, Schachter, Brodie, NEJM 2011;365:919-26

Case 1

- Slide not available

Case 2

- Slide not available

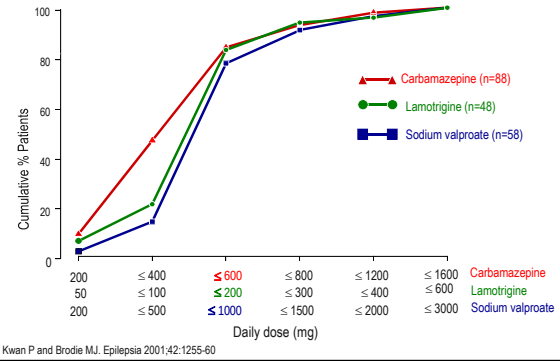
Case 3

- Slide not available

What is "Adequate" Dose?
Case 4

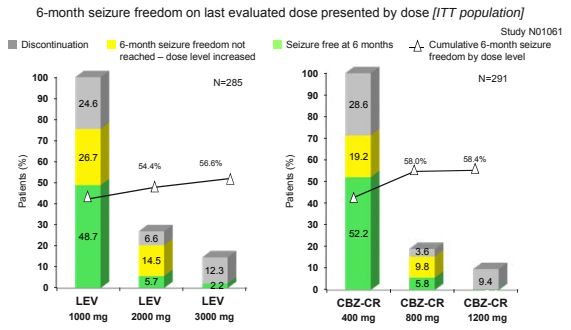
- Slide not available

Dose of First AED in Seizure-Free Patients



Kwan P and Brodie MJ. Epilepsia 2001;42:1255-60

LEV vs CBZ-CR in Newly Diagnosed Adults with Partial-onset Seizures



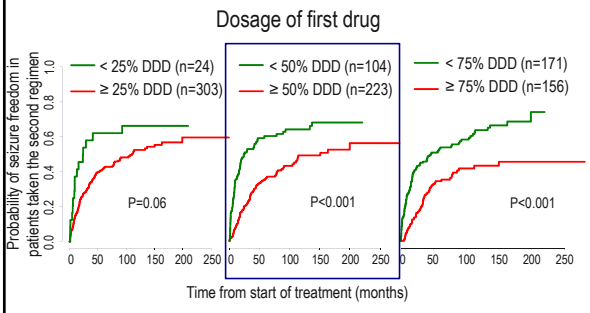
Brodie et al. Neurology 2007;68:402-408

WHO Defined Daily Dose

- Assumed average maintenance dose per day for a drug used for its main indication in adults
  - Carbamazepine 1000mg
  - Phenytoin 300mg
  - Valproic acid 1500mg
  - Topiramate 300mg
  - Levetiracetam 1500mg
  - Lamotrigine 300mg

http://www.whocc.no/ddd/definition_and_general_considera/

Dosage failed of first AED predicted subsequent outcome



Brodie MJ et al, Epilepsia 2013;54:194-8.

DDD, WHO defined daily dose

Uncontrolled ≠ Drug-resistant?

Cross-sectional study at last follow up

Site	Glasgow	Hong Kong
Patient population	"Newly diagnosed" cohort	"Chronic" cohort
Total n	1098	299
Uncontrolled epilepsy	311	194
Drug resistant	136	115
Undefined outcome	175 Failure of only 1 AED: 39% Poor compliance: 34% AE at low dose: 29% Inadequate dose: 29% Social issues: 19% Psychiatric problems: 18% Seizure free <1 year: 13% Patient choice: 8%	79 Inadequate dose/duration: 44% Lack of information: 23% Failure of only 1 AED: 14% Seizure free <1 year: 14% Single seizure relapse: 14%

Hao XT et al, Epilepsy Behav 2013;29:4-6

When Uncontrolled Epilepsy Becomes Controlled

- Unpublished data, slide not available

Hao XT et al, manuscript under preparation

Seizure Control After Drug Manipulation

- Unpublished data, slide not available

Hao XT et al, manuscript under preparation

Conclusion

- 60-65% of patients with new onset epilepsy will become seizure free with medications
- Failure of two AEDs may imply drug resistance and should prompt referral to specialist center
- "Pseudoresistance" must be ruled out
- A substantial proportion of patients with seemingly uncontrolled epilepsy could become seizure free with further AED adjustment
- Dose increase alone seems to be as effective as drug change (add on or substitution)

CAN POLYPHARMACY BE RATIONAL?

Josiane LaJoie, MD
Associate Professor of Neurology and Pediatrics
NYU Langone Medical Center

Disclosures

- Will briefly discuss some medications that are not FDA approved

Learning Objectives

- To understand a rational approach to combing anti-epileptic medications
- To understand how to apply these approaches to patients with specific seizure types and epilepsy syndromes

Refractory Epilepsy

- About 1/3 of patients with epilepsy (PWE) have drug resistant epilepsy
  - Significant morbidity and mortality
- After 2 monotherapy trials, combination therapy can be helpful
- Combination therapy can be successful in about 30% of patients

Brodie J neurol 2005
Mohanraj and Brodie, Epil behavior 2005

Options for Refractory patients

- Medication
- Surgery
  - Resective
  - Vagal Nerve Stimulation, Responsive Neurostimulation
- Diet
  - Ketogenic
  - MCT
  - Atkins
  - Low Glycemic

Back to basics…

- Confirm the diagnosis!!!!!
  - Mimickers
    - Syncope, cardiac, arrhythmia, non-epileptic events
- Confirm Seizure Type
  - Partial vs. Generalized
  - Not sure?
  - Unknown?
  - New seizure type?
    - Consider repeat EEG, VEEG with medication withdrawal
- Medication Issues
  - Wrong Drug (s), Wrong Dose (s) ???, Compliance
- Life Style Issues
  - Alcohol/Drug use, Stress/Sleep Deprivation

What is polypharmacy?

- Is the concurrent use of multiple medications by an individual
- Not unique to epilepsy
  - Has been used in other complex conditions
  - Migraine
  - Neuropathic pain
  - Hypertension
  - HIV
  - Oncology

Polypharmacy-Rational Rules

- **Rational**:
  - Medications selected should have supra-additive efficacy, without worsening of side effects.
  - Patient's condition and quality of life should be **improved**.
- **Problematic**: when there is increased risk of drug interactions and adverse effects negatively affects patient compliance, clinical condition and quality of life.

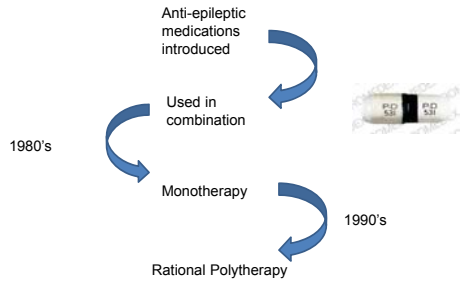
Polypharmacy in epilepsy

- First appeared in the medical literature more than 150 years ago.

"The combinations of bromide with other drugs are of much value in treatment of epilepsy. In many cases a greater effect is produced by the combination than by other drugs given alone"

William Gowers, 1881

Treatment in epilepsy
Treatment paradigms are constantly in flux



How to put medications together???

Combining medications-How many???

- 332 patients on polytherapy
  - 86% controlled on two drugs
  - 13% controlled on three drugs
  - 1% (3) controlled on four drugs

Stephen and Brodie, Seizure. 2002; 11:349-351

- Refractory localization related epilepsy patients
- 193 patients
  - About 10% of patients on **3** drugs achieved seizure freedom
  - **0** patients on four drugs were fully controlled
  - Adverse events increased as number of medications increase

Pelota et al, 2008. Seizure 17:276-80

How to combine AEDs….

- Conventional wisdom suggests combining AEDs with different mechanisms of action is more likely to produce seizure freedom and less side effects than prescribing those with similar or overlapping pharmacological properties.

AED Mechanisms of Action

Sodium Channel blockers
- Fast inactivated state
  - Phenytoin
  - Carbamazepine
  - Lamotrigine
  - Oxcarbazepine
  - Eslicarbazepine
- Slow inactivated state
  - Lacosamide

Synaptic vesicle protein 2A modulation
- **Levetiracetam**

Carbonic anhydrase inhibition
- **Acetazolamide**

Multiple targets
- Sodium Valproate
- Felbamate
- Topiramate
- Zonisamide
- Rufinamide

Calcium Channel blockers
- Low voltage (T) activated channel
  - Ethosuximide
- High voltage (P/Q)activated channel
  - Gabapentin
  - Pregabalin

GABA-ergic drugs
- Prolongs chloride channel opening
  - Barbiturates
- Increased frequency of chloride channel opening
  - Benzodiazepines
- Inhibits GABA transaminase
  - Vigabatrin
- Blocks synaptic GABA reuptake
  - Tiagabine

AEDs and MOA

- Potassium channel opener
  - Ezogabine/retigabine
- Selective AMPA/Kainate antagonist
  - Perampanel

WHAT IS THE EVIDENCE???

Early studies, older AEDs

- Showed that:
- 1) Combinations of AEDs were superior in terms of efficacy (and toxicity) than AEDs used alone
- 2) Combinations were most effective when two drugs had differing mechanisms of action (phenobarbital and phenytoin)
- 3) Less successful were combinations of AEDs with similar mechanisms (phenytoin with carbamazepine)

Bourgeois, B 1986, Morris et al, 1987

Deckers et al

- There is evidence that AED polytherapy based on MOA may enhance effectiveness.
- Combining a Na channel blocker with a drug enhancing GABAergic inhibition appears to be advantageous.
- Combining two GABA mimetic drugs or combining an AMPA antagonist with an NMDA antagonist may enhance efficacy, but tolerability is sometimes reduced.
- Combining two Na channel blockers seems less promising.

Epilepsia 2000.41(11): 1364-74

Human Studies

- The most successful two drug combination in lab studies appears to a be a single mechanism drug combined with an AED known to possess multiple mechanisms of action.
- There are arguments for combining a sodium channel blocker with a drug possessing Gaba-ergic properties or one known to have multiple mechanisms of action.

Deckers et al. Epilepsia 1997; 38:570-5
Kwan and Brodie. Seizure 2000; 9: 464-8
Deckers et al, Epilepsia 2000.41(11): 1364-74

Lamotrigine substitution study Brodie et al

- Multicenter
- 347 patients, uncontrolled epilepsy on VPA, CBZ, PHT, PB
- Lamotrigine added and if improved, substituted
- Responder rate was higher in patients with idiopathic tonic-clonic seizures (61%) than partial (43%)
- Addition of LTG to VPA (64%) produced a significantly better response that its addition to CBZ(41%), PHT (38%)
  - Seen for partial and tonic clonic seizures

Epilepsy Res. 1997 (423-32)

Lamotrigine substitution study Brodie et al

- Side effects:
  - CBZ group: Dizziness and diplopia
  - PHT: nervousness and ataxia
  - VPA group: rash and tremor

Epilepsy Res. 1997 (423-32)

Follow-up studies had similar results.

Found that co-administration of VPA and lamotrigine was more effective than when used alone.

Pisani et al Epilepsia 1999; 40:1141-6

Stephen et al

- 63.6 % with partial epilepsy
- 36.4% with primary generalized epilepsy
- **81.3 %** of patients were controlled on **TWO** AEDs.
- 10 most common effective duotherapies all contained AEDs with different MOA, many possessing multiple mechanisms.
  - Most successful was VPA and lamotrigine

Stephen et al

- **17.5%** were seizure free on **three** AEDs
  - Most successful triple combination
  - VPA, lamotrigine, topiramate
  - VPA, lamotrigine, levetiracetam
- For patients who were seizure free, no difference if localization related or primary generalized.

Severe Myoclonic Epilepsy of Infancy (SMEI)

- Malignant epilepsy syndrome
- Seizures appear first year of life, early refractory nature
- Cognitive impairments

Stiripentol in SMEI

- Inhibitor of cytochrome P 450
  - In rodents, shown to inhibit synaptosomal uptake of GABA.
  - Direct allosteric modulator of the $GABA_A$ receptor
- Chiron et al, 2000
  - Randomized, placebo controlled, add on trial
  - Stiripentol added to VPA and clobazam vs. placebo
  - 15/21 patients (71%) responded on drug
    - 50% reduction in clonic or tonic-tonic seizures.
  - 1/20 patients responded on placebo
  - 9 seizure free on drug, 0 in placebo group
  - SE-drowsiness, anorexia-50% improved with dose adjustment.
  - NOT FDA APPROVED

Stiripentol

- Perez et al 1999
  - 212 patients
  - Found good response in those with partial seizures (57% responded, 14% seizure free.)
  - 49% responded at 3 months.(40% at one month)
  - 10% seizure free
  - 9% worsened
  - 50% of SMEI responded were also on Clobazam.
  - Symptomatic partial epilepsy responded better than cryptogenic
  - Partial patients were also receiving carbamazepine (75%)

Topiramate in SMEI

- Used Topiramate as add on therapy in uncontrolled SMEI patients
- 36 patients
- 94% were receiving VPA, VPA + Clobazam and Stiripentol
  - 78% showed more than 50% reduction in frequency of GTCs and Status Epilepticus
  - 8% had more than 50% increase.
  - 17% seizure free x 4 months
  - SE: GI and behavioral disturbances.
  - 17% stopped due to AE or lack of efficacy.

Kroll-Seger et al, Neuropediatrics, 2006; 37: 325-329

Topiramate and SMEI

- 18 refractory patients
- Median number of AEDs 2.2
- 14 on VPA
- 6 on Primidone
- 3 on CLB
- 2 on LTG, CBZ
- 1 on DPZ, PB
- When TPM added
- 72% had >50% reduction in seizure rate, 50% had >75% seizure reduction rate and 16.6% were seizure free.
- Response slightly better in partial than in generalized seizures.
- Most dramatic response was with atypical absences

Nieto-Barrera et al. Seizure. 2000;9:590-4.

Topiramate and SMEI

- 18 patients (2-21 years), refractory, different seizure types
- Topiramate added to one or two other baseline drugs
  - 14 VPA, 4 CLB, 7 PB, 3 FBM, 2 nitrazepam, 2 CZP,
  - CBZ, LTG, Gabapentin all 1 each
  - 16.7% seizure free
  - 55.5% had > 50% seizure decrease
  - No seizure worsening
  - Response better in GTCs in comparison to complex partial and myoclonic seizure
  - *Studies are suggestive, but did not report responsiveness across AEDs.

Coppola et al, Epilepsy Research. 2002; 45-8

SMEI

- Potential pitfalls
  - Can be worsened by vigabatrin, lamotrigine, carbamazepine.
- Pharmacological data
  - Some reports state that adding Topiramate to stiripentol may theoretically pose some problems of interactions
  - Both inhibit cytochrome P450
  - May potentiate actions of other drugs by increasing its plasma concentration

Patsalos and Perruca. Lancet Neurol, 2003; 2: 347-356.
Than et al. Arch Pediatrics. (:1142-9, 2006

Lennox Gastaut

- Known as a medically refractory epileptic encephalopathy
- VPA usually first line
- Felbamate was shown to be effective in a controlled and blinded trial
  - Particularly effective in controlling atonic seizures.
  - Lamotrigine and Topamax show efficacy in controlled trials.
  - Topiramate and Lamotrigine were shown to have a synergistic effect

Felbamate Study Group 1993
Stephen and Brodie1998

LGS and Clobazam

- 217 patients, ages 2-60 with LGS
- Randomized to placebo or Clobazam (different dosing)
  - Average weekly drop seizure rates:
    - 12.1% placebo
    - 41.2% (0.25 mg/kg/day)
    - 49.4% (0.50 mg/kg/day)
    - 68.3% (1 mg/kg/day)
  - 50% of all patients were receiving VPA

Ng et al. Neurology, 1011. Neurology 1473-81

Rufinamide and partial seizures

- Double blinded, placebo controlled, randomized trial with Rufinamide, adolescents and adults
- Add on to Carbamazepine, VPA, Lamotrigine, Gabapentin Phenytoin, Phenobarbital
  - Rufinamide subjects taking cbz had median reduction in partial seizures of 12.3% which was not significantly different from placebo
  - Rufinamide subjects without CBZ in their AED regimen had a median reduction of 29.2% compared with 0.7% in placebo subjects whose regime did not include CBZ.
- Needs further study.

Brodie et al, 2009

Lennox Gastaut Syndrome

- Cochrane Review (randomized controlled trials)
  - Concluded that lamotrigine, topiramate and felbamate may be helpful adjunctive medications.
  - Lamotrigine vs. placebo (-32% vs. -9%)
  - Felbamate vs. placebo (-19% vs. + 4%)
  - Topiramate vs. placebo (-21% vs. -9%)-not statistically significant
    - All have been shown to decreased atonic seizures
    - Frequency of GTC decreased mostly with lamotrigine and felbamate
    - Atypical absences difficult to quantify
    - Rufinamide helpful in total seizure reduction (-32.7% vs. -11.7%)
      And tonic clonic seizures (-42.5% vs. +1.4%)

Arzimanoglou, et al. Lancet Neurology. January 2009, volume 8:82-93

Other combinations

- VPA and Ethosuximide for childhood and juvenile absence
  - *Rowan et al Arch Neurol 1983 40:797-802*
  - *Covani et al, 1992*
  - *Santavuori. Acta Neruol Scand Suppl 97:41-8, 1983*
- Carbamazepine with VPA or Vigabatrin for partial seizures
  - *Brodie ML and Mumford JP 1999.*
- Vigabatrin with Tiagabine for partial seizures
  - *Leach and Brodie, 1994*
- VPA and levetiracetam for Myoclonic seizures
  - *Brodie et al, 2011*
- Juvenile Myoclonic Epilepsy
  - Lamotrigine and Topiramate for JME
    - *Arch Neurol 60: 1100-1105, 2003*
  - Lamotrigine and Valproic Acid
    - *Hussain and Sankar, Semin Pediatric Neurol 18:171-8, 2011*

Lacosamide

- MOA is the selective enhancement of sodium channel slow inactivation.
- Multiple studies data have revealed that Lacosamide can be usefully combined with traditional sodium blocking agents (fast inactivation)-lamotrigine, oxcarbazepine, carbamazepine, phenytoin

Sake et al. CNS drugs 2010, 24; 1055-58
Ben-Menachem et al. Epilepsia. 2007; 48 (7):1308-17
Cung et al. Epilepsia. 2010. Jun; 51(6): 958-67
Halasz et al. Epilepsia. 2009. Mar; 50 (3) 443-53
Rosenfeld et al. AAN, 2009

Study Limitations

- Many published investigations can be incomplete
  - Fail to account for pharmacokinetic interactions
  - Lack of consistency of drug level monitoring
  - Lack of assessment of toxicity
  - Lack of evidence of brain penetration

Limitations

- Literature review for clarification about AED polytherapy and AEs.
- Most studies eliminated due to incomplete reporting of concomitant medications (dosing, number of patients, serum levels) or AE
- Only 15/118 analyzed
- Hard to quantify SE in terms of severity, just frequency
- No mention of development of tolerance.
- Poor reporting on impact on quality of life.

Deckers et la. Epilepsia 38 (5): 570-575, 1997

Polytherapy doesn't only apply to medications

- Kossoff et al, 2007
- Retrospective, multicenter study of children
- KTG diet or modified Atkins and VNS for medically refractory epilepsy (varied etiologies)
- 30 children, median duration was one year.
- After 3 months, 70% had seizure reduced by > 50% when combined
- 62% had improvement within the first month.
- No SE reported
- No particular efficacy with AEDs
  - Concluded that diet and VNS were synergistic in effect.

Concluding thoughts

Think of combining medications with **varying** MOA
Avoid using medications with similar side effect profile
Drug **substitution** instead of addition!
Consider each patient's individual clinical characteristics
Be mindful of possible drug interactions, side effects

Future

Efforts must turn to understanding pharmacoresistance and applying methods to reverse the properties of epileptogenic brain chemistry, seizure generation and propagation.

Need progress in better defining phenotypes and genotypes which may provide more insight into the tailoring of treatment options for patients with epilepsy

Need more studies combining different pharmacologic and non-pharmacologic options.

Need larger studies reporting on synergism

Need further studies on alternative therapies (CBD, immunomodulating agents)

Update on Nonpharmacologic Treatments

Christopher T. Skidmore, MD
Thomas Jefferson University

December 4, 2015

1

Disclosure

Neuropace: Site PI
Supernus: Consultant

2

Clinical Case

- BH has now failed three AEDs
- He has 3-4 complex partial seizures per month
- He is experiencing trouble with cognition, which increased with his current AED regimen

- What are your options for treatment?

3

Learning Objectives

- To understand diet therapy alternatives
- To understand the role of the Responsive Neurostimulator
- To understand the role of the vagal nerve stimulator
- To review deep brain stimulation for epilepsy

4

Diet Therapy

5

Diet Therapy

- Ketogenic Diet
  - Established treatment
  - Fat consumption 90% of diet
- Modified Atkins Diet
  - Carbohydrate consumption 5-10% of diet
  - Fat consumption 60-65% of diet
- Low Glycemic Index Diet
  - Carbohydrate consumption 20-30% of diet
  - Fat consumption 60-70% of diet

6

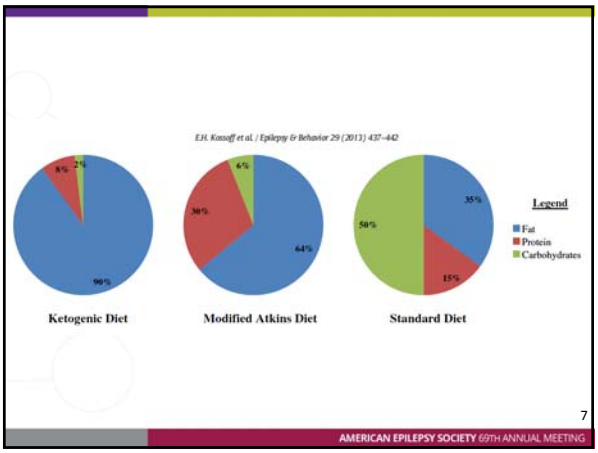


Table 2
Differences between the ketogenic and the modified Atkins diet.

	Ketogenic diet	Modified Atkins diet
Calories (% recommended daily allowance)	Restricted (75%) or matched	Unrestricted
Fluids (")	Measured to RDA	Unrestricted
Fat	85%–90%	~60%
Protein	15%	~30%
Carbohydrates	5%	~10%
Fasting period	Occasionally done	Not used
Admission to hospital	Typically done	No
Meal plans computer-created	Yes	No
Foods weighed and measured	Yes	No (carbs monitored)
Sharing of food at family meals	No	Yes
Ability to eat foods made in restaurants	No	Yes
"Low carbohydrate" store-bought products	Not used	Allowed sparingly
Intensive education provided	Yes	No
Dietitian involvement	Yes	Typically yes
Multiple studies over many years showing benefits	Yes	Yes, recently

Kossoff EH et al. Epilepsy & Behavior. 2013

Diet Therapy

- Outcomes
  - Approximately 50% of patients have a 50% reduction in seizures
- Side Effects
  - Constipation
  - Elevated lipids
  - Weight Loss

Felton EA, Cervenka MC. Epilepsia. 2015

NeuroStimulation

Neurostimulation

- Vagal Nerve Stimulation
  - FDA approval 1997
  - Indication: Refractory focal epilepsy > age 12
- Responsive Neurostimulator
  - FDA approval 2013
  - Indication: Refractory focal epilepsy in adults
- Deep Brain Stimulator – Anterior Nucleus
  - Approved in Europe (2010) and Canada (2012)
  - Indication: Refractory focal epilepsy in adults

Vagus Nerve Stimulator

- Old data
  - Side Effects: Hoarseness and cough
  - Open loop system
  - Magnet for on demand stimulation
- New data
  - Aspire SR
    - Option for auto-stimulation feature
    - Provides stimulation based on change in heart rate

Vagus Nerve Stimulator

- Stimulator
  - Triggers based on % change in heart rate (HR)
    - Range 20-70%
  - Slow moving average used for baseline HR
- Two Clinical Studies (E36 and E37)
  - Total of 51 patients

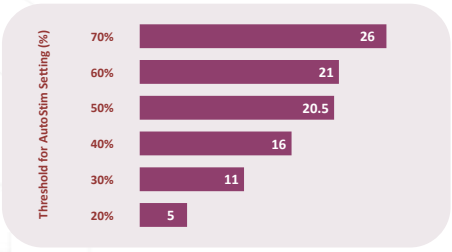
Study Design and Schedule

Implant & 2-week recovery	1- to 3-week stimulation titration period	3- to 5-day Epilepsy Monitoring Unit (EMU) stay -AutoStim ONLY-	Up to 24-month follow-up
All VNS Therapy naive patients	Titration to 0.75 mA	**At the beginning of EMU stay:** • Disabled Normal and Magnet Mode • Enabled AutoStim Mode **During:** • Investigators annotated electrographic onset and offset of each seizure • 3 minute exercise test once a day **Discharge:** • Normal Mode, Magnet Mode and Automatic Stimulation were altered as desired	Clinical data collected with Normal, Magnet, and AutoStim Modes enabled

Data on File, Cyberonics, Inc. Houston, TX.

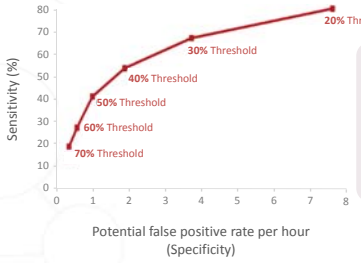
Lower Threshold for AutoStim resulted in earlier stimulation...

Median stimulation latency (seconds post seizure onset)



Data on File, Cyberonics, Inc. Houston, TX.

Threshold for AutoStim - Sensitivity vs Specificity



Sensitivity and potential false positive rate for each Threshold for AutoStim

34 patients, 170 seizures

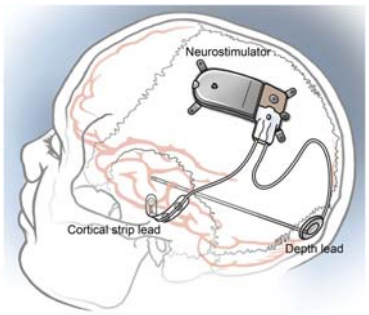
VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

Vagus Nerve Stimulator

- Outcomes
  - Safety comparable to normal device
  - Successfully detected HR change and triggered
  - Will this lead to better clinical outcomes?

Responsive Neurostimulator

Figure 1 Implanted RNS neurostimulator and NeuroPace cortical strip and depth leadsCopyright owned by NeuroPace, Inc; no permissions for use are required.



Gregory K. Bergey et al. Neurology 2015;84:810-817

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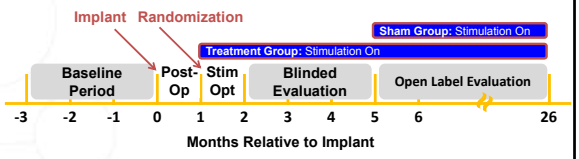
Responsive Neurostimulator (RNS)

- Pivotal Trial
  - 191 Patients
  - Double Blind, Sham Stimulation
  - Refractory Focal Epilepsy
    - No more then 2 localizations



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RNS - Demographics

Characteristics	All implanted (n = 191)	By randomization group: Treatment (n = 97)	Sham (n = 94)	p Value*
Sex, % female	48	48	47	0.820
Mean ± SD age, y (range)	34.9 ± 11.6 (18-66)	34.0 ± 11.5 (18-60)	35.9 ± 11.6 (18-66)	0.239
Mean ± SD years with epilepsy (range)	20.5 ± 11.6 (2-57)	20.0 ± 11.2 (2-57)	21.0 ± 12.2 (2-54)	0.546
Mean ± SD no. of AEDs at enrollment (range)	2.8 ± 1.2 (0-8)	2.8 ± 1.3 (1-8)	2.8 ± 1.1 (0-6)	0.926
Mean ± SD no. baseline seizures per day (range)	1.2 ± 2.2 (0.1-12.1)	1.2 ± 2.0 (0.1-10.5)	1.2 ± 2.4 (0.1-12.1)	0.875
Mesial temporal seizure onset (vs other), %	50	49	50	0.943
Two seizure foci (vs one), %	55	49	62	0.089
Prior therapeutic surgery for epilepsy, %	32	35	30	0.437
Prior intracranial EEG monitoring, %	59	65	53	0.098
Prior VNS, %	34	31	36	0.443

Abbreviations: AED = antiepileptic drug; VNS = vagus nerve stimulation.
*p Value for across-group comparisons (treatment compared to sham) using 2-sample t test and χ^2 (for proportions).

Morrell MJ. Neurology. 2011

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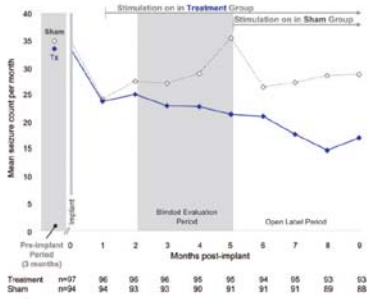
Mean Disabling Seizures by Month



Morrell MJ. Neurology. 2011

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Long Term Treatment with RNS

- Pivotal Trial and Feasibility Study Combined
  - 230 patients enrolled; 191 patients active follow-up
  - Median % reduction
    - Year 3: 60
    - Year 6: 66
  - % Responder Rate
    - Year 3: 58
    - Year 6: 59
  - Safety/Side Effects
    - Intracranial Hemorrhage 4.7%
    - Implant Site Infection 9.4%
    - Death 4.3%
      - 2 Suicide, 1 Status, 1 Lymphoma, 7 SUDEP

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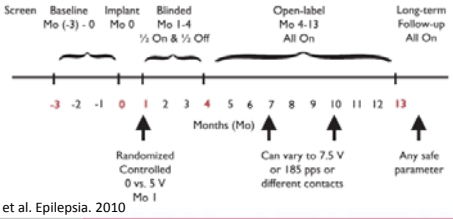
Deep Brain Stimulator
Anterior Nucleus of the Thalamus

24

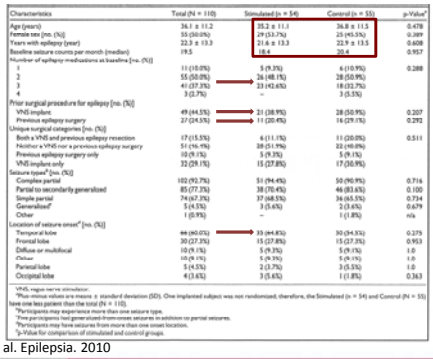
SANTE Trial

- Pivotal Trial
  - 110 Patients
  - Double Blind, Sham Stimulation
  - Refractory Focal Epilepsy



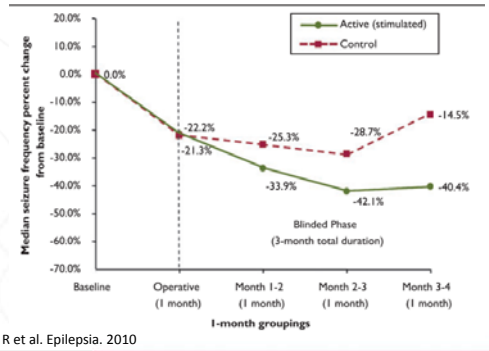
Fisher R et al. Epilepsia. 2010

SANTE - Demographics



Fisher R et al. Epilepsia. 2010

Median Seizure Frequency Percent Change



Fisher R et al. Epilepsia. 2010

DBS – SANTE Trial

- Safety/Side Effects
  - Paresthesias (18.2%), Implant Site Pain (10.9%), Implant Site Infection (9.1%)
  - Intracranial Hemorrhage 4.5%
  - Death (4.5%): 1 Suicide, 4 SUDEP
- Long Term Treatment
  - 105 patients enrolled; 30 discontinuations
  - Median % reduction
    - Year 1: 41
    - Year 5: 69
  - % Responder Rate
    - Year 1: 43
    - Year 5: 68

Fisher R et al. Epilepsia. 2010; Salanova V et al. Neurology. 2015

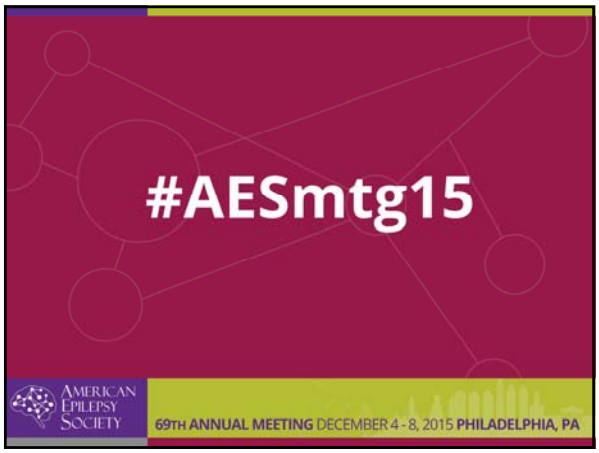
Neurostimulation Comparison

Study	Number of Patients (Number Active Group)	% Seizure Reduction, Blinded (95% confidence intervals)	% Responder Rate, Blinded	% Responder Rate, 1 year
VNS – E03	114 (54)	24.5 (14.1-34.9)	31	
VNS – E06	196 (94)	27.9 (21-34.8)	23.4	35
RNS	191 (97)	37.9 (27.7-46.7)	29	43
DBS	109 (54)	NR	NR	43

Fridley J. Neurosurg Focus. 2012

Conclusions

- BH has many non-pharmacologic options
- Alternatives to the ketogenic diet are effective and more practical for every day life
- Neurostimulators offer an alternative to medical therapy that does not require daily effort on behalf of the patient
- Which option is better?


#AESmtg15
American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disease Modifying Treatments for Epilepsy

Andrew J. Cole, M.D.
Professor of Neurology
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December 5, 2015

American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosures

Precisis AG
Abide Therapeutics
Sage Therapeutics
Blueprint Medicines
The Medicines Company
Eisai
Mindgraph Medical
Nestec
Neuropace
UCB

Learning Objectives

- Become familiar with the concept of disease M
- modification in epilepsy
- Describe the intrinsic difficulties of studying disease modification in epilepsy
- Become familiar with probably, possible, and unproven examples of disease modification in epilepsy.

Impact on Clinical Care and Practice

- Disease Modification is a treatment goal
- Disease Modification is difficult to demonstrate
  - Time course is long
  - Anticonvulsant efficacy is a confounder
  - Endpoints amenable to modification are diverse
- Strategies to achieve disease modification require thinking beyond anti-seizure treatment

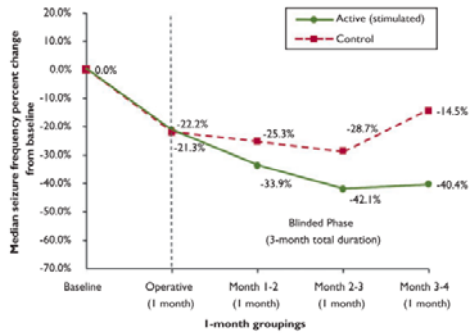
Disease Modification in Epilepsy

- Epilepsy Definition
  - Recurrent unprovoked seizures, or an enduring predisposition to same
- Disease Modification Definition
  - Modification of the expression of the disease
  - Modification on the course of the disease
  - Modification of the co-morbidities integral to the disease

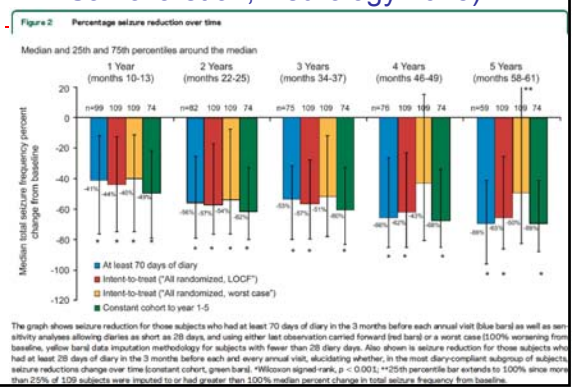
Talk Outline

- Disease modification demonstrated: Stimulation therapy
- Disease modification well studied (in animals): Absence epilepsy
- Disease modification possible: Epileptic encephalopathies
- Disease modification un-proven: Epileptogenesis

SANTE Median Seizure Frequency



Sante LT F/U Data Salnova et al., Neurology 2015)



Seizure Control after Battery Depletion using DBS

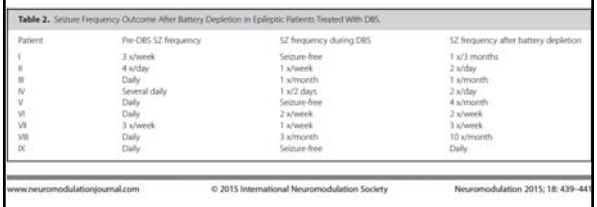


Table 2. Seizure Frequency Outcome After Battery Depletion in Epileptic Patients Treated With DBS.

Patient	Pre-DBS SZ frequency	SZ frequency during DBS	SZ frequency after battery depletion
I	3 x/week	Seizure-free	1 x/3 months
II	4 x/day	1 x/week	2 x/day
III	Daily	1 x/month	1 x/month
IV	Several daily	1 x/2 days	2 x/day
V	Daily	Seizure-free	4 x/month
VI	Daily	2 x/week	2 x/week
VII	3 x/week	1 x/week	3 x/week
VIII	Daily	3 x/month	10 x/month
IX	Daily	Seizure-free	Daily

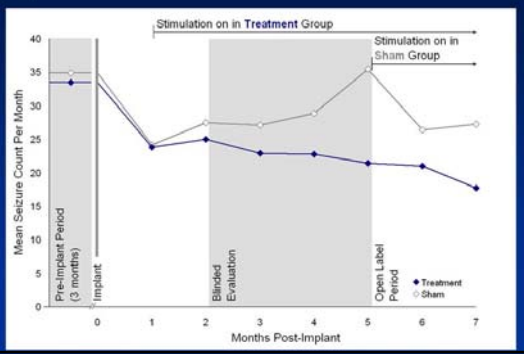
www.neuromodulationjournal.com © 2015 International Neuromodulation Society Neuromodulation 2015; 18: 439–443

Seizure Outcome After Battery Depletion in Epileptic Patients Submitted to Deep Brain Stimulation. Arthur Cukiert, MD, PhD*†; Cristine Mella Cukiert, MD*†; Jose Augusto Burattini, MD*‡; Alessandra de Moura Lima, MD‡ MGH Epilepsy Service

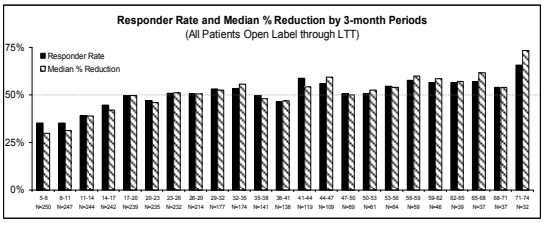
Early Treatment Modifies Spike-and-Wave Trait Expression in Rodents

Early treatment suppresses the development of spike-wave epilepsy in a rat model. Hal Blumenfeld*,†,‡, Joshua P. Klein*, Ulrich Schridde*, Matthew Vestal*, Timothy Rice*, Davender S. Khera*, Chhitij Bashyal*, Kathryn Giblin*, Crystal Paul-Laughinghouse*, Frederick Wang*, Anuradha Phadke*, John Mission*, Ravi K. Agarwal*, Dario J. Englot*, Joshua Motelow*, Hrachya Nersesyan*, Stephen G. Waxman*, and April R. Levin* MGH Epilepsy Service

Pivotal Trial: Mean Disabling Seizures, Observed Data (N=191)



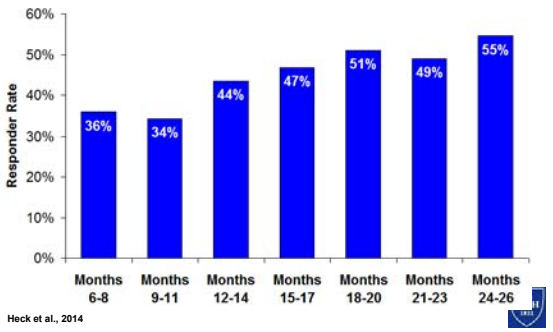
Seizure reduction is sustained over long term follow-up



- N values reflect maximum follow-up times
- Mean patient follow-up is 3.3 years

Pivotal Study Responder Rate

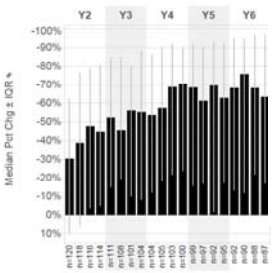
All subjects receiving stimulation



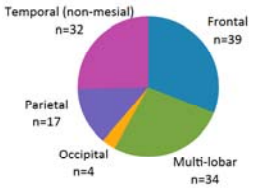
Heck et al., 2014

Neocortical Long-term Follow-up

Median Percent Reduction: All Neocortical Onset Patients



Lobe of seizure onset



Jobst et al., AES 2015

MGH Epilepsy Service

Epileptic Encephalopthy

- Childhood syndromes characterized by
  - Spikes
  - Seizures
  - Cognitive delay/regression
  - Frequently activated by sleep
  - May be idiopathic, symptomatic or cryptogenic
- Spikes and seizures each may affect development
- Expression of epilepsy is often age dependent, e.g. CSWS, LKS
- Cognitive dysfunction is often enduring

MGH Epilepsy Service

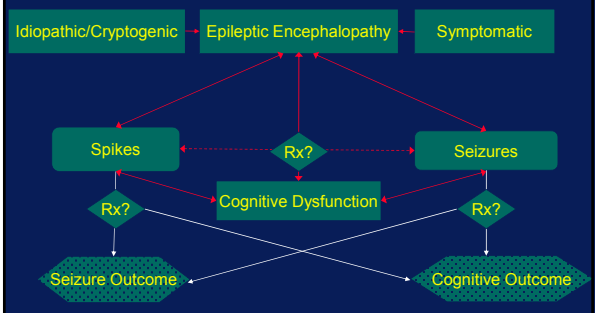
Is Treatment Disease Modifying?

- Early Rx, and response to Rx, associated with better cognitive outcome
- Findings independent of specific Rx (Pellock et al, 2010)
  - ACTH
  - Vigabatrin
  - Ketogenic diet
  - Epilepsy surgery
- Symptomatic etiologies more resistant to Rx and have poorer cognitive outcomes
- Impossible to conduct randomized studies

Chapman, Sprecchio, Shinnar and Holmes, 2015

MGH Epilepsy Service

Seizures, Spikes and Epileptic Encephalopathy

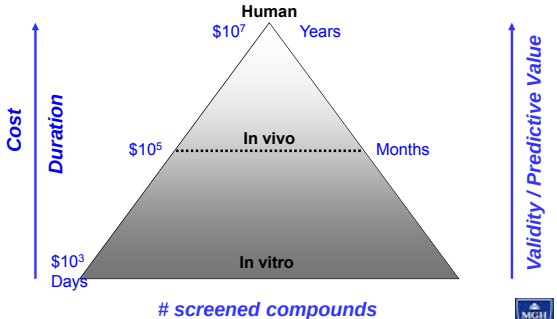


The MGH Epilepsy Center

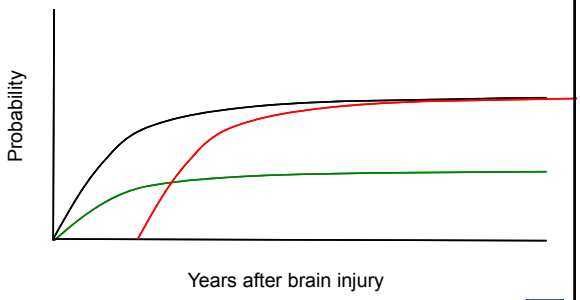
AJC 12/1/2015

Screening drugs in chronic epilepsy

anticonvulsant / neuroprotective / **antiepileptogenic**



Anticonvulsant vs. Antiepileptogenic: Shift to the Right vs. Reduced Maximum



Characteristics of the Ideal Clinical Trial Population

- Defined precipitating event
- Knowledge of interaction between severity of precipitating event, likelihood of developing epilepsy, and latency of epilepsy onset
- Rate of post-event epilepsy high enough to limit n, but low enough that Rx is not futile
- Survival and follow-up assured
- Events of interest capable of being reliably detected, differentiated and reported

Incidence of Epilepsy after Head Injury

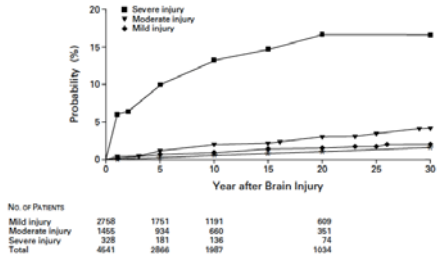


Figure 1. Cumulative Probability of Unprovoked Seizures in 4541 Patients with Traumatic Brain Injuries, According to the Severity of the Injury and the Incidence of Seizures in the General Population.

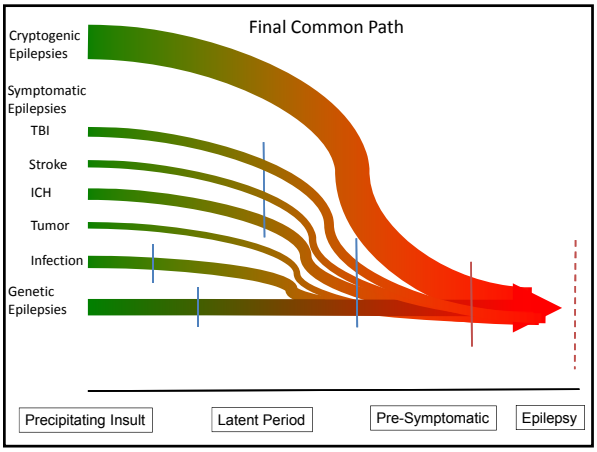
Annegers et al., NEJM, 1998

Potential Antiepileptogenisis Trial Populations

Precipitating Event	Homo-geneity	Abundance of patients	Knowledge of Natural Hx	Definition of time of event	Likelihood of survival	Incidence of post-event epilepsy
Stroke	+	+++	++	+	++	5%
Hemorrhage	++	++	++	++	++	7.5-10%
Tumor	+	+++	++	-	-	NA
Trauma	++	++++	++++	++++	++	15-25%
Status	+	+	++	++++	++	NA
Infection	+	+	+	++	++	NA

Power and Cost Calculations

Placebo	Drug	Absolute	Relative	Power	N	Retention Rate	Modified N	Cost @ $30,000/subject
20.0%	10.0%	10.0%	50.0%	0.8	502	0.7	718	$21,528,355.84
20.0%	10.0%	10.0%	50.0%	0.9	672	0.7	961	$28,820,360.40
20.0%	12.0%	8.0%	40.0%	0.8	785	0.7	1121	$33,638,056.00
20.0%	12.0%	8.0%	40.0%	0.9	1051	0.7	1501	$45,031,813.12
30.0%	15.0%	15.0%	50.0%	0.8	293	0.7	419	$12,558,207.57
30.0%	15.0%	15.0%	50.0%	0.9	392	0.7	560	$16,811,876.90
15.0%	7.5%	7.5%	50.0%	0.8	712	0.7	1017	$30,498,504.11
15.0%	7.5%	7.5%	50.0%	0.9	953	0.7	1361	$40,828,843.90
5.0%	2.5%	2.5%	50.0%	0.8	2386	0.7	3409	$102,259,690.25



Conclusions

- Disease modification consists of changing the expression, severity, duration or co-morbidities of epilepsy (not mutually exclusive)
- Low class evidence for disease modification exists in device-based treatment literature
- Supportive evidence for disease modification comes from animal studies early treatment of S+W
- Suggestive data for DM exists in epileptic encephalopathy literature (VGB, ACTH, ketogenic diet)
- Important DM targets (antiepileptogenisis after insults known to cause epilepsy) remain largely unexplored

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Disease Modifying Treatments for Epilepsy

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Disclosures

- Consultancies
  - Precisis AG
  - Abide Therapeutics
  - Sage Therapeutics
  - Blueprint Medicines
  - The Medicines Company
  - Eisai
  - Mindgraph Medical
  - Nestec
  - Neuropace
  - UCB

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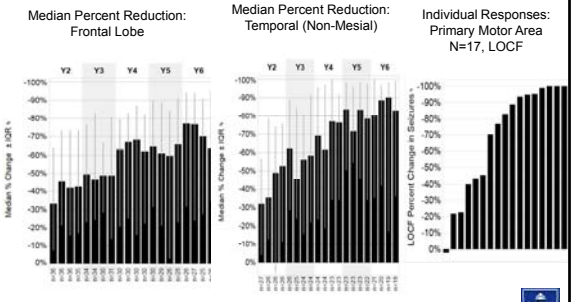
Neocortical Long-term Follow-up



Jobst et al., AES 2015

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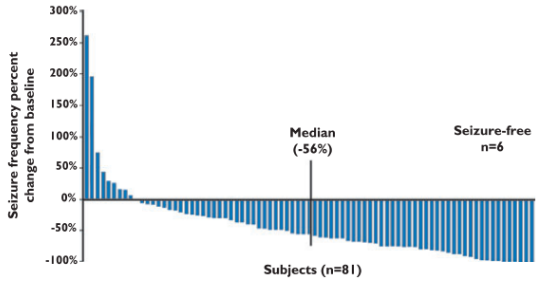
SANTE Seizure Frequency Reduction (>25 month follow-up, n=81)



Epilepsy Therapy Symposium: Conclusions

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December 5, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Name of Commercial Interest

Wiley
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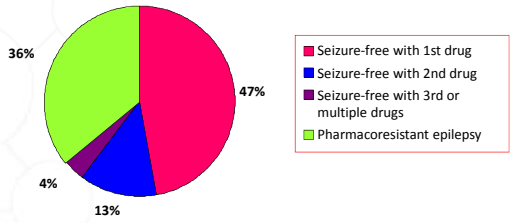
NINDS

Learning Objectives

- To analyze how many patients are drug resistant and uncontrolled
- Review strategies to move more of your uncontrolled patients into the controlled group
- Answer the ARS questions

Response to Antiseizure Medication: 60% seizure free with 1st or 2nd Drug

Previously Untreated Epilepsy Patients (n=470)



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.

How many persons with epilepsy are uncontrolled or truly drug resistant?

Of uncontrolled

- Glasgow "newly diagnosed" 136/311 43%
- Hong Kong "chronic" 115/194 59%
- Chengdu "prospective" 37/342 11%

Of all persons with epilepsy

- Glasgow "newly diagnosed" Total N=1098
  - 12% drug resistant (n=136)
  - 16% uncontrolled (n=175)
- Hong Kong "chronic" Total N=299
  - 38% drug resistant (n=115)
  - 26% uncontrolled (n=79)
- Chengdu "prospective"?

Hao XT et al, Epilepsy Behav 2013;29:4-6

Do we really know? Why so variable?

- The drug resistant population is well defined
  - Is not shifting categories to AED-controlled
  - Being drug resistant is independent of developed or developing world AED exposure
- The proportion of drug resistant and uncontrolled patients is truly unclear
  - Depends on population
  - Depends on health care
  - Depends on study design

Response to Antiseizure Medication: 1098 patients

67% n=737 seizure free for one year

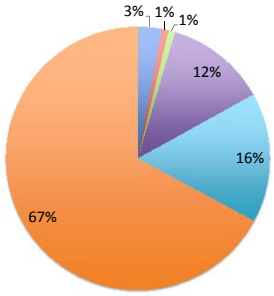
16% n=175 Uncontrolled

12% n=136 Drug resistant

3% n=32 Deaths including SUDEP and suicide

1% n=9 Not enough info

1% n=9 AED Trials



Hao XT et al, Epilepsy Behav 2013;29:4-6

Response to Antiseizure Medication: 1098 patients if 17% of the Uncontrolled became seizure free with adding an AED +/- AED dose increase

70% n=767 seizure free for one year

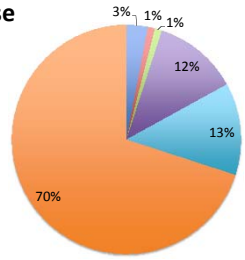
13% n=145 Uncontrolled

12% n=136 Drug resistant

3% n=32 Deaths including SUDEP and suicide

1% n=9 Not enough info

1% n=9 AED Trials



Hao XT et al, Epilepsy Behav 2013;29:4-6

Do you know what proportion of your patients are drug resistant or uncontrolled or seizure free?

- AAN Quality measure # 7 relates to drug resistance…
  - Was the patient referred for a consultation at a comprehensive epilepsy center?
- How many of your uncontrolled patients can become seizure with more vigilance and TLC?
  - At least 17% due to increasing dose or adding another drug
  - Perhaps at least that much again if compliance can be increased
  - If depression is reduced
  - If patient understanding is increased

ARS Question #1

Which of the following statements is true?

1. Carbamazepine, lamotrigine, levetiracetam and gabapentin have similar effectiveness in newly diagnosed focal epilepsy-False
2. Evidence favors lamotrigine for females with childhood absence epilepsy-False
3. Valproate has unsurpassed efficacy in generalized epilepsies, but risks related to childbearing potential are a major concern-True
4. Rational antiseizure drug selection includes the concept of additive effects such as using pregabalin and gabapentin in combination-False

ARS Question #2

Which of the following statements is true?

1. "Pseudoresistance" refers to the concept of patients under-reporting good seizure control-False
2. A substantial proportion of patients (~33%) with seemingly uncontrolled epilepsy could become seizure free with further AED adjustment-False
3. In clinical trials, approximately half of patients starting the ketogenic diet, the modified Atkins diet, or the low glycemic index treatment have a >50% reduction of seizures-True
4. Levetiracetam and zonisamide have been shown in animal studies and human clinical trials to have anti-epileptogenic properties-False

Thanks to JoLynn and to all the speakers for sharing their knowledge and ideas with us!
Go forth and stamp out disease!

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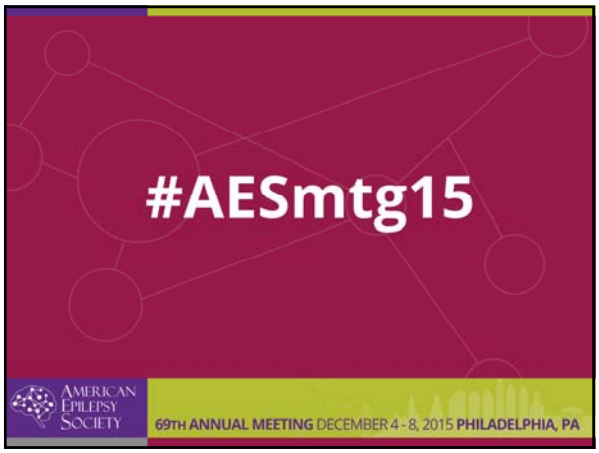
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