Epilepsy Specialist Symposium
Treating the New Onset Epilepsy Patient

Symposium Co-Chairs:
Gregory Krauss, M.D.

and

Scott Mintzer, M.D.

Friday, December 6, 2013
Convention Center – Ballroom C, Level Three
8:30 a.m. – 11:30 a.m.
OVERVIEW
While many epilepsy specialists spend much time seeing patients with longstanding disease, the group of new-onset epilepsy patients represents a distinct population with specific treatment concerns. This symposium will address the various issues involved in treating those with new-onset epilepsy, including considerations of when a patient should be treated, the evidentiary basis for drug choice, treatment prognosis, and specific factors relating to various subgroups (such as children and the elderly).

LEARNING OBJECTIVES
- Manage patients with new onset epilepsy across the age spectrum, based on preferred practices, peer reviewed literature, and published practice parameters
- Recognize new-onset epilepsy syndromes and prescribe anti-seizure medications using published evidence regarding treatment of specific syndromes.

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

PROGRAM
8:30 – 8:45 am Introduction
Gregory L. Krauss, M.D.
8:45 – 9:15 am Treating New Onset Epilepsy: The Perspective from a Longitudinal Study
Bernd Pohlmann-Eden, M.D., Ph.D.
9:15 – 9:45 am Drug Choice in New-Onset Epilepsy
Tracy A. Glauser, M.D.
9:45 – 10:15 am New-Onset Epilepsy in Children
Dave F. Clarke, M.B.B.S.
10:15 – 10:45 am New Onset Epilepsy in the Elderly
Ilo E. Leppik, M.D.
10:45 – 11:15 am Treatment Prognosis for New-Onset Epilepsy
Scott Mintzer, M.D.
11:15 – 11:30 am Conclusions
Gregory L. Krauss, M.D.

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 3.0 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 3.0 hours of Category 1 credit for completing this program.

Nurses: EDUPRO Resources LLC is an approved provider of continuing nursing education by Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing
Center’s Commission on Accreditation. EDUPRO is also an approved provider by the California Board of Registered Nursing, provider number CEP-14387. Nurses who participate in selected AES programs can receive up to 30.75 contact hours. To successfully complete the activities, nurses are required to complete the evaluations for each session attended and to access the Medical Education Evaluator to claim Credit.

Nurses may claim up to 3.0 contact hours for this session.

Pharmacists: Extension Services in Pharmacy at the University of Wisconsin-Madison School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Selected portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Program numbers assigned to those presentations are found in the AES Annual Meeting Program Book. Credit is based on documented program attendance and on-line completion of a Program Evaluation/Assessment.

To obtain CE credit, go to the Division of Pharmacy Professional Development: http://ce.pharmacy.wisc.edu. No CE credit will be provided beyond January 15, 2014.

You may also access the AES virtualToteBag for more detailed instructions and to complete the CE Statement of Credit Request Form.

The ACPE Universal Activity Number (UAN) is 0073-9999-13-092-L01-P and provides 3.0 contact hours.

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 Credit™.

ABPN Core Competencies
The American Board of Psychiatry and Neurology has reviewed the Epilepsy Specialist Symposium and has approved this program as part of a comprehensive lifelong learning program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Core Competencies: Comprehensive Patient Care, Medical Knowledge, and Professionalism

ACKNOWLEDGEMENT
This program is supported in part by an educational grant from Eisai Inc. and Lundbeck 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

Dave Clarke, M.B.B.S.
Dr. Dave Clarke received his medical degree at the University of the West Indies. He completed his residency at Overlook Hospital, an affiliate of Columbia University College of Physicians and Surgeons, and received his Pediatric Neurology training at the University of Michigan Medical Center, and Neurophysiology (Epilepsy and Sleep) at the Hospital for Sick Children, University of Toronto, in Toronto, Canada. Dr. Clarke is currently Director of the Comprehensive Epilepsy Program at Dell Children’s Medical Center in Austin, TX. Recently Dr. Clarke was elected President of the Epilepsy Society of the Caribbean and he is an active member of the Board for the North American Commission.

Dave Clarke, M.B.B.S. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Cyberonics-VNS discussions Lundbeck- Speaker Bureau for Onfi and Sabril; as Participation in Foundation or Not-for-Profit Organizations from AES, CNS, ILAE

Tracy Glauser, M.D.
Tracy A. Glauser, MD, is Professor of Pediatrics and Director of the Comprehensive Epilepsy Center at Cincinnati Children's Hospital Medical Center. Dr. Glauser trained in pediatrics at The John Hopkins Hospital, child neurology at The Children’s Hospital of Philadelphia and epilepsy and electroencephalography at St. Louis Children’s Hospital. Dr. Glauser has co-authored more than 140 articles. He has been the principal investigator on multiple NIH grants including the Childhood Absence Epilepsy clinical trial involving 29 pediatric centers around the United States. Dr. Glauser's fields of expertise are pediatric epilepsy, clinical trials, clinical pharmacology and pharmacogenetics.

Tracy Glauser, M.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Questcor Pharmaceuticals, Inc., Supernus Pharmaceuticals; as Consulting/Advisory Board Activity from AssureRx, Questcor Pharmaceuticals, Inc., Lundbeck Research USA, Sunovion, Supernus Pharmaceuticals, Eisai, Inc., ucb Pharma, and Upsher-Smith Laboratories; as Honoraria from Commercial Sources from Questcor Pharmaceuticals, Inc., Lundbeck Research USA, Sunovion, Supernus Pharmaceuticals, Eisai, Inc., UCB Pharma, and Upsher-Smith Laboratories; as Company Ownership (incl. personally managed stocks and stock options, excluding mutual and managed funds) from AssureRx (stock options, equity); as Royalties/Income from Patents from AssureRx; as Intellectual Property Ownership from AssureRX; as Federal/State/Not-for Profit Funding from 2U01-NS045911 (PI: Glauser) U10-NS077311 (PI: Glauser, Khatri) R01NS062756 (PI: Holland) R01LM011124 (PI: Pestian) R01NS065840 (PI: Vannest).

Gregory Krauss, M.D. (Co-Chair)
Gregory Krauss, MD is a Professor Neurology at the Johns Hopkins University. His educational training background is: Harvard undergraduate; OHSU medical school; Johns Hopkins neurology residency and epilepsy fellowship. He conducts research over a range of clinical topics including developing new acute and chronic antiepilepsy therapies, drug safety, generic drug quality, epilepsy and driving risks, treatment of early Alzheimers Disease, neurogenesis in migration disorders. He is author of a multimedia EEG training atlas and teaches extensively in the US and internationally.

Gregory Krauss, M.D. discloses receiving support as Consulting/Advisory Board Activity from Eisai Laboratories; as Consulting/Advisory Board Activity from UCB Pharma; as Honoraria from Commercial Sources from Medscape CME program UCB patient and family scholarship selection panel; as Research Funding from For Profit Commercial Sources/Principle Investigator from UCB Pharma, Vertex, Sunovian, SK Bios, Eisai, Upsher Smith; as Federal/State/Not-for Profit Funding from RC2AG036419. National Institute of Aging, NIH.; as Participation in Foundation or Not-for-Profit Organizations from Epilepsy Foundation of America--Chesapeake
Ilo Leppik, M.D.
Dr. Ilo E. Leppik is a Professor of Pharmacy and Neurology at the U. of Minnesota. He is the past President of the AES. He maintains an active practice with MINCEP Epilepsy Care. Honors: The Penfield Prize from MNI, and the 2007 William G. Lennox Award from AES. From 1986 to 2006, Dr. Leppik was a founding and managing editor of Epilepsy Research. NIH funding is for using naturally occurring canine status epilepticus as a translational platform for new drugs and epilepsy. He has widely published over 225 peer-reviewed articles. He wrote Contemporary Diagnosis and Management of the Patient With Epilepsy (650,000 copies) and Epilepsy: A Guide to Balance Your Life, sponsored by the AAN

Ilo Leppik, M.D. discloses receiving support as Consulting/Advisory Board Activity from Eisai, Lundbecke, USL, UCB; as Honoraria from Commercial Sources from Eisai.

Scott Mintzer, M.D. (Co-Chair)
Scott Mintzer is Associate Professor of Neurology and Director of the Epilepsy Monitoring Unit at the Jefferson Comprehensive Epilepsy Center and Thomas Jefferson University. He trained in Neurology at the University of Michigan and in Epilepsy and Clinical Neurophysiology at the University of California Los Angeles. He is current co-chair of the Neuropharmacology Special Interest Group of the AES and is a contributing editor to Epilepsy Currents. He is the author of numerous publications and book chapters on the medical and surgical treatment of epilepsy. His major research interest is in the metabolic effects of antiepileptic drugs.

Scott Mintzer, M.D. discloses receiving support as Consulting/Advisory Board Activity from Participated in advisory boards for Eisai, Lundbeck, Acorda, Upsher-Smith, and UCB Consulting work on clinical trials through the Epilepsy Study Consortium for the following companies: Upsher-Smith, Pfizer, Sunovion, Eisai, SK, Vertex.; as Federal/State/Not-for Profit Funding from NIH K23NS058669.

Bernd Pohlmann-Eden, M.D., Ph.D.
Dr. Bernd Pohlmann-Eden, Professor of Neurology, obtained his MD and PHD degree from the University of Heidelberg (Germany). He was staff member of the Faculty Mannheim (Univ. Heidelberg) from 1986-2000 and Director of the Epilepsy Program since 1990. In 1994, he was a visiting scientist at Harvard Medical School in Boston. From 2000 to 2002, he was a visiting professor at the Epilepsy Service of the Toronto Western Hospital, Canada. In 2003 he became Head and Chair of the Epilepsy Program in Bethel, Germany, Director of the Epilepsy Research Society and Professor of Public Health. Since 2008, he is Director of Epilepsy Program Development in Halifax, Dalhousie University, Canada.

Bernd Pohlmann-Eden, M.D., Ph.D. has nothing to disclose.

Jack Lin, M.D. (CME Reviewer)
Jack J. Lin, MD is an Associate Professor of Neurology at the University of California at Irvine and the Director of the Clinical Neurophysiology/Epilepsy Fellowship. Dr. Lin’s research focuses on the cognitive and psychiatric comorbidities of epilepsies. Using advanced neuroimaging techniques, he has uncovered neurodevelopmental impacts of new-onset pediatric epilepsies, examined limbic network alterations associated with mood disorders in temporal lobe epilepsy, and delineated links between syndrome specific structural abnormalities and cognitive deficits. He serves as a grant reviewer for the Epilepsy Foundation, an NINDS Benchmark Steward, and a member of several AES committees.

Jack Lin, M.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from UCB Pharma; as Federal/State/Not-for Profit Funding from NINDS K23 (K23NS060993).
Paul Levisohn (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.

Paul Levisohn, M.D. discloses receiving support as Consulting/Advisory Board Activity from CME medical content consultant to AES staff.; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai (clinical trials); as Federal/State/Not-for Profit Funding from NIH/NINDS: Childhood Absence Epilepsy, PI. NeuroNEXT, PI.; as Participation in Foundation or Not-for-Profit Organizations from Professional Advisory Board, Epilepsy Foundation; Co-chair, Advisory Committee National Center for Project Access; Consultant to AES.

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The Medical Education Evaluator® is an online system that allows any attendee to self-manage the process of completing course evaluations, tracking educational credits and printing out the CME or nursing certificate.

Pharmacy credit and certificates are available separately as noted above

Log on to the Evaluator via the AES website at www.AESnet.org. Once you are on the Evaluator, you will be asked to enter your MyAES ID # and password. You must then complete the evaluations and claim credit for the sessions you attended. The certificate(s) are saved to your personal account page and you may print the certificate(s) in PDF format at any time.

To help support this process, attendees who want CME will be asked to pay the following rates:

- **Member Fees:**
  - $50 through January 17, 2014
  - $75 January 18 – February 28, 2014

- **Non-member Fees:**
  - $75 through January 17, 2014
  - $100 January 18 – February 28, 2014

The online Evaluator will be left open through February 28, 2014. You must complete the evaluations and credit tracking by that date.

By completing this information online, attendees greatly assist the Council on Education and Annual Meeting Committee with important needs assessment data whereby the AES can further plan and address educational gaps to meet the needs of our learners.

A meeting attendance certificate will be available for international meeting attendees at the registration desk.

**Handouts**
Handouts for the educational symposia are available to print in the AES virtualToteBag. Paper handouts will not be provided on site.
Introduction: Treating patients with new onset epilepsy

Gregory Krauss, MD,
Professor of Neurology
Johns Hopkins University

Learning Objectives

• Translate specialist skills into treating patients with new onset epilepsy
• Appreciate how prognosis, patient factors and needs of special populations influence treatment of new onset epilepsy

New onset seizures–vs- chronic epilepsy care

• Patient subjective/emotional reactions
  – Education/Coping
  – Adaptation/Participation in Care
• Clinical patterns
  – Seizure types
  – Treatment need & treatment responses

Disclosure

Eisai, UCB Pharma, Sunovian, SK Bios, NINDS, Upsher Smith
Eisai, UCB Pharma
Lundbeck

Evaluating and treating new onset epilepsy with an expert’s eye

“...in the beginner’s mind there are many possibilities, in the expert’s mind there are few.”

Translating epilepsy experts’ skills into treating new onset epilepsy

1) New onset epilepsy
2) Establishing the diagnosis
3) Effective counseling
4) Treatment selection
5) Monitoring for SE, seizures, impact on driving, work, life
6) Establishing the arc of epilepsy
Seizure freedom/drug resistance/remission?
Evidence based decision making for new onset epilepsy:
Cumulative probability of second seizure for epileptogenic lesion found on MRI when prior
CT was normal.

Case Study: New onset epilepsy

- 69 year old female retired nurse
- Initial seizure out of sleep—
  - Husband found thrashing, screaming, unresponsive.
  - Duration 4 minutes with 30 minutes of recovery.
  - No treatment; normal laboratories & head CT in ED.
- Seizure recurrence 4 months later
  - 2 seizures in a single day
    - Treatment with levetiracetam, but severe irritability.
    - Treatment with pregabalin with apathy, depression, and poor coordination;
      similar symptoms on topiramate
    - Discontinued treatment. Feels well off anticonvulsants.
- PMH:
  - Hypertension and previous 35 years history of smoking.
  - Routine and 48-hour EEG performed elsewhere: normal.
  - Brain MRI: normal except for microvascular disease bilaterally.

CASE STUDY: New onset epilepsy

Questions:
Retired nurse with new onset epilepsy & major AEs with three AEDs. She now refuses additional
treatment. Her local neurologist frightened her that SUDEP was possible if she did not receive treatment.

Would you strongly recommend AED treatment, eg. Lamotrigine? Y/N

Her only plea is to drive to church early in the morning on local roads; is this OK? Y/N

Treating new onset epilepsy:

- Population Study of First Seizures & Need for Treatment
  - Berndt Pohlmann-Eden, MD, PhD
- Drug Choices in New-Onset Epilepsy
  - Tracy A. Glauser, MD
- New-Onset Epilepsy in Children
  - Dave F. Clarke, MBBS
- New Onset Epilepsy in the Elderly
  - Ilo Leppik, MD
- Treatment Prognosis for New-Onset Epilepsy
  - Scott Mintzer, MD
- Conclusion & Audience Discussion
Treating NOE: The Perspective From a Longitudinal Study
December 6, 2013
Bernd Pohlmann-Eden MD PhD
Co-Director Epilepsy Program
Professor of Neurology, Pharmacology and Psychology, Dalhousie University, Halifax, Canada & Rupprechts-Karl-University Heidelberg, Germany
b.pohlmann-eden@dal.ca

Learning Objectives
• Create awareness around the opportunity to study ("observe") epilepsy at an early stage and to arrive at an appropriate individualized treatment decision
• Recognize the value of a longitudinal prospective approach (First Seizure Clinic) to better understand individual and collective treatment response

Illustrative case 42 y/o M
• First generalized-tonic seizure 05_2009 with preceding subtle staring for few seconds only
• 2 weeks later referral and first evaluation at Halifax First Seizure Clinic
• Evidence for a prolonged complex-partial seizure in 04_2009, questionable SPS preceding
• Social Hx: Accountant, married, 2 children
• Family Hx: Paternal uncle epilepsy
• Neuroexam N; EEG left temp SW; MRI demo

Treating New-onset Epilepsy
The Perspective of a Longitudinal Study

• Illustrative Case
• The Why
• Terms are critical
• Preliminary results
• Conclusions

Illustrative case 42 y/o M
• Dg: New-onset epilepsy Periventricular Heterotopia
• Treatment initiated LEV BID 750mg
• MRI demo T2_FSE Periventricular Heterotopia

Disclosure
None
Treating New-onset Epilepsy

The Perspective of a Longitudinal Study

The Why

Most of our knowledge about treatment response originates from retrospective cross-sectional studies and potentially has led to misperceptions & misconceptions.

The initial choice of AED in NOE is crucial: Monitoring the individual treatment course will allow new insights in individual time pattern and scenarios of pharmacoresistance.

Individual analysis is as important as group data.

Etiology and Responder Rate

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Responder Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic focal</td>
<td>35%</td>
</tr>
<tr>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>45%</td>
</tr>
<tr>
<td>Tumor</td>
<td>46%</td>
</tr>
<tr>
<td>Inf. seq.</td>
<td>36%</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td>24%</td>
</tr>
<tr>
<td>Dysplasia</td>
<td></td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>11%</td>
</tr>
<tr>
<td>Dual Pathology</td>
<td>3%</td>
</tr>
</tbody>
</table>

Semah et al. Neurology 1998;51:1256-1262

The unknown journey from A to B

Clinical Epileptogenesis

- Impact of syndrome-inherent factors
- Impact of seizure activity
- Impact of therapy
- Impact of genetics
- Impact of interplay of all these factors

First Seizure

Second Seizure

Chronic Epilepsy

Tissue changes over time

Research is integral part

Opportunities

Longitudinal approach

- Risk factors for seizure recurrence after 1st seizure (etiology / EEG)
- Analyze development of pharmacoresistance in the concert of treatment intervention and structural and functional data

Clinical Epileptogenesis

Opportunities

Longitudinal approach

- Risk factors for seizure recurrence after 1st seizure (etiology / EEG)
- Analyze development of pharmacoresistance in the concert of treatment intervention and structural and functional data
Treating New-onset Epilepsy

The Perspective of a Longitudinal Study

- Illustrative Case
- The Why
- Terms are critical
- Preliminary results
- Conclusions

Terms are critical

Epilepsy = “2 unprovoked seizures”?
Not clarified role of time interval between the 2 events

Diagnosis of Epilepsy after one seizure only?

“…a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure”

Terms are critical

New-onset Epilepsy ≠ Newly diagnosed Epilepsy

“First seizure” patients often have New-onset epilepsy or Newly Diagnosed Epilepsy

Fisher et al. 2005: Epileptic Seizures and Epilepsy: Definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau For Epilepsy (IBE). Epilepsia 46: 470-472

New-onset Epilepsy
- First scan (T=0)
  - Hippocampal structure
  - Hippocampal volume

First scan (T=0): MRI scan
Hippocampal structure
Hippocampal volume

Follow-up (T=12 mo)
Pharmacoresistance
NAA or NA/Cr as a predictor of PR
EEG
MR spectroscopy
Diffusion tensor imaging

Follow-up (T=18 mo)
Pharmacoresistance
NAA or NA/Cr as a predictor of PR
EEG
MR spectroscopy
Diffusion tensor imaging

Multifactorial predictive model for PR

Pohlmann-Eden, Crocker, Schmidt: Epilepsia. 2013, 54 Suppl 2:75-9

Illustrative Case

Terms are critical

Not clarified role of time interval between the 2 events

Newly diagnosed Epilepsy

“First seizure” in presence of preceding subtle simple partial seizures

Critical role of distinguishing epileptic deja-vue from non-epileptic deja-vue

New-onset Epilepsy
- First scan (T=0)
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First scan (T=0): MRI scan
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Critical role of distinguishing epileptic deja-vue from non-epileptic deja-vue
Terms are critical

New-onset Epilepsy ≠ Newly diagnosed Epilepsy

“The magnitude of the incidence of new onset epilepsy and the incidence of newly diagnosed epilepsy will differ, because the measures have different numerators. For new onset epilepsy, the numerator includes people identified at their second unprovoked seizure. In contrast, the numerator for newly diagnosed epilepsy (NDE) includes both new onset epilepsy and people with more than two unprovoked seizures who are first diagnosed with epilepsy during the study period...”.

Thurman DJ et al (2011) ILAE Commission on Epidemiology: Standards for epidemiological studies and surveillance of epilepsy. Epilepsia 52(Suppl. 7):2–26

NOE defined as early stage of epilepsy

New-onset Epilepsy

Subcategory

Newly diagnosed Epilepsy

NOE New-onset epilepsy with evidence for ≥ 2 seizures within ≤ 1st year (this includes frequent preceding simple or complex partial seizures)

NDE Newly diagnosed epilepsy with evidence of ongoing seizures for > > 1 year.

Time domain suggested in the definitions of NOE and NDE, rather than the absolute number of seizures, which often is hard to assess.


Pohlmann-Eden AES 2013

Scenarios of newly diagnosed epileptic seizures

FIRST SEIZURE (FS), NOE and NDE

Treating New-onset Epilepsy

The Perspective of a Longitudinal Study

• Illustrative Cases
• The Why
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"First Seizure" Presentations Nova Scotia

Halifax First Seizure Clinic  HFSC

Epidemiology: Incidence of First Seizures (FS) General Population 40 – 70 / 100,000 per year

400 – 700 NEW FS-cases per year in a population of 950,000 in Nova Scotia

Referral Network FS - HFSC 100-120 New Referrals per year

Bernd Pohlmann-Eden (MD) Karen Legg (NP) Candice Crocker (Res Assoc)
Main Criteria for AED choice

- Syndrome (focal/ generalized)
- Efficacy
- Safety profile
- Tolerability
- Low interaction profile
- Speed of action
- Age / gender
- Comorbidities
- Special issues (weight, cognition)
- Drug cost / coverage

Initiating treatment in New-Onset Epilepsy

- Drug of choice should have long-term safety, good tolerability, high seizure freedom rate, low interaction potential, allow good quality of life

  Note: New AEDs seem to fulfill this profile better

- This is specifically important for patients with New-onset epilepsy as most patients might stay on the first AED for a long-time

- Always "individualized and tailored"
  Usually after 2 or more unprovoked seizures

Initiating treatment after 1 seizure?

Scenarios in which AED treatment should be considered

**High risk profile for seizure recurrence**
- Remote symptomatic lesion and corresponding epileptiform EEG activity
- High risk lesion (abscess, sinus thrombosis)

**Neurobiological concept of “epilepsy”**
- Presence of epileptiform potentials on EEG, specifically generalized epilepsy

**Medical and social conditions which lead to additional harm as a result of further seizures**, examples:
- Polytrauma with spinal cervical fracture
- Severe osteoporosis
- Preventable renal failure due to myoglobinuria
- Patients on antiagulation
- Patients with high risk of loss of employment with further seizure

Initial treatment: Partial onset epilepsy

Center-specific preferences AED

- Lamotrigine
- Levetiracetam
- Carbamazepine

Based on expert opinion (level 3), SANAQ (level 8) study, and level A studies (Class I RCT 12-48 week studies)

Initial treatment: Primarily generalized epilepsy

Center-specific preferences AED

- Lamotrigine
- Valproate
- Levetiracetam
- Topiramate

Based on expert opinion (level 3), SANAQ (level 8) study, and level A studies (Class I RCT 12-48 week studies)
Number of Seizures in treated NOE

<table>
<thead>
<tr>
<th>Seizures</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>11%*</td>
</tr>
<tr>
<td>4</td>
<td>6%*</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>8%*</td>
</tr>
<tr>
<td>No treatment</td>
<td>8%</td>
</tr>
</tbody>
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* all within last 12 mths

Choice of AEDs used in New-onset Epilepsy

<table>
<thead>
<tr>
<th>AED</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Phenytoin*</td>
<td>37%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>19%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>18%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>15%</td>
</tr>
<tr>
<td>Valproate</td>
<td>6%</td>
</tr>
<tr>
<td>Others</td>
<td>5%</td>
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</table>

* Often started by ER physician

Switch to Second AED in NOE < first 6 month

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switch in</td>
<td>37.7%</td>
</tr>
<tr>
<td>Safety/SE</td>
<td>41.4%</td>
</tr>
<tr>
<td>Not efficacious</td>
<td>27.5%</td>
</tr>
<tr>
<td>Other reasons</td>
<td>31.1%</td>
</tr>
</tbody>
</table>

> 50% switches: PTH to other AED (LEV in 75%)

Seizure-freedom after 6 months (1st follow-up)

<table>
<thead>
<tr>
<th>Status</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sz free with AED</td>
<td>64%</td>
</tr>
<tr>
<td>Sz free no AED</td>
<td>2%</td>
</tr>
<tr>
<td>One further sz</td>
<td>10%</td>
</tr>
<tr>
<td>Disabling sz &lt;=1/mth</td>
<td>12%</td>
</tr>
<tr>
<td>Disabling sz &gt; 1/mth</td>
<td>2%</td>
</tr>
<tr>
<td>SPS only</td>
<td>10%</td>
</tr>
</tbody>
</table>

Failure of 2 or more AED suggesting Pharmacoresistance (PR)

149 patients with NOE and new, Interim Analysis: occurrence of PR, Mexico follow-up 2.5 years (2006-2012)

Highly variable pattern of PR with sz free intervals of > 1 year (demo)

11.2% only fulfilled criteria for PR

Patterns of Pharmacoresistance

33 y/o old female Nonresistant seizure, ECDI

56 y/o old female Nonresistant

69 year old male Nonresistant
Treating New-onset Epilepsy

The Perspective of a Longitudinal Study

- Illustrative Case
- The Why
- Terms are critical
- Preliminary results
- Conclusions

Conclusions

Treating New-Onset Epilepsy: The Perspective of a Longitudinal Study

- Precise definitions of first seizure, new-onset epilepsy and newly diagnosed epilepsy in their temporal pattern are critical preconditions to interpret data in prospective studies dealing with early stages of epilepsy.
- Despite a center-specific "rational algorithm" for individualized AED choice initiating treatment in NOE, "reality check" in our study showed that patients frequently end up with suboptimal AED as a result of health care system specifics or referral patterns. The epileptologist in charge may have to consider an early switch to a more appropriate AED.

Pharmacoresistance (PR) CANNOT be expected to always occur within the first year of diagnosis of NOE. It is much more likely that patterns of PR are much more variable and phases of seizure-freedom of 1 to 2 years or even longer may not exclude long-term PR. This observation has major counseling implications.

Thanks...!
Drug Choice in New-Onset Epilepsy

December 6, 2013

Tracy A. Glauser, M.D.
Director, Comprehensive Epilepsy Center
Cincinnati Children’s Hospital Medical Center

Learning Objectives
Participants will be able to:
• Recognize the variety of factors that influence antiepileptic drug selection in new onset epilepsy
• Evaluate the strength of clinical trial evidence for antiepileptic drugs’ efficacy/effectiveness for different seizure types
• Assess the benefits and limitations of epilepsy randomized controlled trials

The Start of the Modern Journey for AED Efficacy/Effectiveness

“Who can forget that without putting pen to paper, Locock…turned the tide of hopelessness that…had immersed the epileptic...”

Sir Charles Locock

The Start of the Modern Journey for AED Efficacy/Effectiveness

“For doctors, there is this moral: Never miss a scientific meeting on epilepsy, and give close attention to the discussion”

Medical Societies.

ROYAL MEDICAL & CHIRURGICAL SOCIETY.
TUESDAY, MAY 11TH, 1857.

Sir C. Locock, President, in the Chair.

ANALYSIS OF FIFTY-TWO CASES OF EPILEPSY OBSERVED BY THE AUTHOR.

BY EDWARD H. SHEYKING, M.D., F.R.C.P.,
PHYSICIAN TO THE LATER DEPARTMENTS OF THE MENTAL AID OF THE NURSES, BY THE NURSES, AND ASSISTANT-PHYSICIAN TO THE MILD HOSPITAL.

Disclosure

<table>
<thead>
<tr>
<th>Nature of Financial Relationship</th>
<th>Name of Company(ies)</th>
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<td>Research Support</td>
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<tr>
<td>Employment (with a commercial interest)</td>
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<td>Speaker’s Bureau Membership</td>
<td>Questcor Pharmaceuticals, Inc., Supernus Pharmaceuticals</td>
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<tr>
<td>Advisory Committee Membership, Honorarium Recipient, Consultancy</td>
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<tr>
<td>Review Panel Membership</td>
<td>NINDS</td>
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<td>Board Membership</td>
<td>None</td>
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<tr>
<td>Intellectual Property</td>
<td>AssureRx Health</td>
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<td>Ownership Interests (stock, stock options)</td>
<td>AssureRx Health</td>
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American Epilepsy Society | 2013 Annual Meeting
**Variables That Affect Initial AED Selection**

<table>
<thead>
<tr>
<th>AED-specific variables</th>
<th>Patient-specific variables</th>
<th>Nation-specific variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug type or syndrome efficacy/effectiveness</td>
<td>• Genetic</td>
<td>• AED availability</td>
</tr>
<tr>
<td>• Dose-dependent AEs</td>
<td>• Age</td>
<td>• AED cost</td>
</tr>
<tr>
<td>• Idiosyncratic reactions</td>
<td>• Gender</td>
<td>• Insurance coverage</td>
</tr>
<tr>
<td>• Chronic toxicities</td>
<td>• Co-medications</td>
<td></td>
</tr>
<tr>
<td>• Teratogenicity</td>
<td>• Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>• Carcinogenicity</td>
<td>• Insurance coverage</td>
<td></td>
</tr>
<tr>
<td>• Pharmacokinetics</td>
<td>• Ability to swallow pills/tablets</td>
<td></td>
</tr>
<tr>
<td>• Interaction potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Formulations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Randomized Controlled Trials**

The Environment and Disease: Association or Causation?
- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

**Streptomycin in Tuberculosis Smoking and lung cancer**


**ILAE Evidence Review**

For patients with newly diagnosed or untreated epilepsy, which AEDs have the best evidence for long-term efficacy or effectiveness as initial monotherapy?

8 situations:
1. Partial onset seizure - Adults
2. Partial onset seizure - Children
3. Partial onset seizure - Elderly
4. GTC seizure - Adults
5. GTC seizure - Children
6. Absence seizure - Children
7. BECTS
8. JME

Glauser, Epilepsia. 2013 Mar;54(3):551-63

**ILAE Criteria for Class I Study**

A prospective, randomised, controlled clinical trial (RCT) in a representative population that meets all six criteria:
1. Primary outcome variable: efficacy or effectiveness
2. Treatment duration: ≥ 48 weeks (≥24 wk seizure freedom data for efficacy or >48 wk retention data for effectiveness)
3. Study design: double blind
4. Superiority demonstrated or, for noninferiority trial or failed superiority trials: the study treatment efficacy/effectiveness lower limit (95% CI) is above a 20% lower bound relative to the adequate comparator’s point estimate of efficacy/effectiveness using a per-protocol study population
5. Study exit: not forced by a predetermined number of treatment emergent seizures
6. Appropriate statistical analysis

Glauser, Epilepsia. 2013 Mar;54(3):551-63

**ILAE Criteria for Class II Studies**

- **Class II**: An RCT or meta-analysis meeting all the class I criteria except that:
  1. Treatment duration: ≥24 wks but ≤48 wks
  OR
  2. Failed superiority trials or noninferiority trials: the study treatment’s efficacy/effectiveness lower limit (95% CI) is between the 21% and 30% lower boundary relative to the adequate comparator’s point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups)

Glauser, Epilepsia. 2013 Mar;54(3):551-63
ILAE Criteria for Class III and IV Studies

- **Class III:** An RCT or meta-analysis not meeting the criteria for any class I or class II category

- **Class IV:** Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series or expert reports

Partial Onset Seizures (POS): Summary of Efficacy/Effectiveness Evidence

<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (alphabetic order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS: Adults</td>
<td>4</td>
<td>1</td>
<td>34</td>
<td>Level A: CBZ, PHT, LEV, ZNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: GBP, LTG, OXC, PB, TPM, VGB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: CJP, PRM</td>
</tr>
<tr>
<td>POS: Children</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>Level A: OXC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, PHT, TPM, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: CLB, CJP, LTG, ZNS</td>
</tr>
<tr>
<td>POS: Elderly</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>Level A: GBP, LTG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: TPM, VPA</td>
</tr>
</tbody>
</table>

Determining Level of Evidence

<table>
<thead>
<tr>
<th>Combination(s) of Clinical Trial Ratings</th>
<th>Level of Evidence</th>
<th>Efficacy/effectiveness as initial monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Class I studies OR ≥ 2 Class II studies</td>
<td>A</td>
<td>Established</td>
</tr>
<tr>
<td>1 Class II study</td>
<td>B</td>
<td>Probably</td>
</tr>
<tr>
<td>≥ 2 Class III DB or OL studies</td>
<td>C</td>
<td>Possibly</td>
</tr>
<tr>
<td>1 Class III DB or OL study OR ≥ 1 Class IV clinical studies OR Expert committee, opinions</td>
<td>D</td>
<td>Potentially</td>
</tr>
<tr>
<td>Absence of clinical evidence</td>
<td>E</td>
<td>No data available</td>
</tr>
<tr>
<td>Positive evidence of lack of efficacy/effectiveness or risk of seizure aggravation</td>
<td>F</td>
<td>Ineffective or significant risk of seizure aggravation</td>
</tr>
</tbody>
</table>

Generalized Onset Seizures: Summary of Efficacy/Effectiveness Evidence

<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (alphabetic order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCGS: Adults</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: GBP, LEV, VGB</td>
</tr>
<tr>
<td>TCGS: Children</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, PB, PHT, TPM, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: OXC</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>Level A: VPA, ESM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: LTG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: None</td>
</tr>
</tbody>
</table>

Syndromes: Summary of Efficacy/Effectiveness Evidence

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (alphabetic order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECTS</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: GBP, LEV, OXC, STM</td>
</tr>
<tr>
<td>JME</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Level C: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: TPM, VPA</td>
</tr>
</tbody>
</table>

Randomized Controlled Trials Benefits

- Minimizes bias
- Minimizes impact of variability
- Better information than anecdotal medicine
- Improves chance of getting the “right” answer
Randomized Controlled Trials
Limitations
- RCT may not ask the right question
- Identified treatment effect - large or small?
- Does not explain differential subjects benefit
- Artificial environment
- Management often determined by protocol
- Patients receive encouragement to remain on therapy and maintain compliance

Variables That Affect Initial AED Selection

<table>
<thead>
<tr>
<th>AED-specific variables</th>
<th>Patient-specific variables</th>
<th>Nation-specific variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex type or syndrome</td>
<td>Genetic</td>
<td>AED availability</td>
</tr>
<tr>
<td>efficacy/effectiveness</td>
<td>Age</td>
<td>AED cost</td>
</tr>
<tr>
<td>Dose-dependent AEs</td>
<td>Gender</td>
<td>Insurance coverage</td>
</tr>
<tr>
<td>Idiosyncratic reactions</td>
<td>Co-medications</td>
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<td>Chronic toxicities</td>
<td>Co-morbidities</td>
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<tr>
<td>Teratogenicity</td>
<td>Insurance coverage</td>
<td></td>
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<tr>
<td>Carcinogenicity</td>
<td>Ability to swallow tablets</td>
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<tr>
<td>Pharmacokinetics</td>
<td></td>
<td></td>
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<tr>
<td>Interaction potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Conclusions
- There are few well designed, properly conducted epilepsy clinical trials.
- Absence of evidence does not mean evidence of absence.
- When selecting a patient’s AED, all relevant variables and not just efficacy and effectiveness should be considered

Impact on Clinical Care and Practice
- Recognize and incorporate the variety of factors that influence antiepileptic drug selection in new onset epilepsy
- Improved ability to critically evaluate the strength of clinical trial evidence for antiepileptic drugs’ efficacy/effectiveness for different seizure types
- Improved understanding of the benefits and limitations of epilepsy randomized controlled trials

Factors involved in making a clinical decision

Conclusions
- Guidelines or evidence reviews are additional tools, not the only tool in the clinician’s armamentarium.
- The ultimate judgment for therapy must be made in the light of all the clinical data presented by the patient and by the treatment options that are locally available for the patient and his/her clinician.
New-Onset Epilepsy in Children
December 6, 2013

VIDEO

Dave F. Clarke, MBBS, ABPN (Child Neurology and Sleep), ABCN
Associate Professor of Pediatric Neurology-UTSW, Austin
Director, Dell Children’s Comprehensive Epilepsy Program
Dell Children’s Medical Center of Central Texas

Disclosure
• Cyberonics Speaker Bureau
• Lundbeck Speaker Bureau

Learning Objectives
1. Seizures versus non-epilepsy paroxysms.
2. Pairing childhood Epilepsy Syndromes and constellations with the correct Anti-Epileptic Medications.

The Chronicles of the life of a Patient with “Spells”
• 7 year old who is on the honor roll in school going into 2nd grade.
• At 3-1/2 years of age he began having atypical events — tongue and facial twitching, usually to the left, with occasional articulation difficulties — He has never a secondarily generalized tonic-clonic event.
• Most of his events occur early in the morning (1/3 months).
• Levetiracetam, Topiramate, Lamotrigine, Oxcarbazepine

Question 1: In the Case described:
A. The diagnosis can be assumed by taking a detailed history
B. A routine EEG is diagnostic
C. An overnight EEG often clinches the diagnosis.
D. A and C are correct

Question 2: In the Case described:
A. The patient has non-REM parasomnias
B. Levetiracetam and Oxcarbazepine both have Level A,B efficacy in treating this condition
C. Treatment may not always be necessary in this condition
D. Lamotrigine and Topiramate may be synergistic in stopping his episodes
• Does he have Epilepsy?

• Does he have a defined Epilepsy Syndrome?

• What is the evidence for effective treatment in this or any other Epilepsy Syndrome?

Scope of the problem

• Methods: 127 children seen in a tertiary care First Seizure Clinic. (1 month - 17 years)

• Results:
  – Non-epileptic in 31 (24%) and unclassifiable in two (2%).
  – Pediatrics were more likely to refer true epileptic events (92%) than ED physicians (76%) or family physicians (65%).
  – 15% - developmentally delayed; abnormal neurological exam - 11%.

• Conclusions: One quarter of children were incorrectly diagnosed as having a seizure while the diagnosis of epilepsy was missed in over one-third of children.

Diagnostic inaccuracy in children referred with “first seizure”: Role for a First Seizure Clinic (L. D. Hamblet et al., 2000)

Non-epileptic seizures

<table>
<thead>
<tr>
<th>Paroxysmal SEs</th>
<th>Non-epileptic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized tonic-clonic seizure</td>
<td>Convulsive syncope, *pseudoseizure, *concussive convolution, hyperekplexia, *Carfentanil arousals</td>
</tr>
<tr>
<td>Abnormal seizure</td>
<td>Daydreaming, *pseudoseizure, *Hyperekplexia</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>Myoclonus syncope, *benign sleep myoclonus, *other forms of non-epileptic myoclonus</td>
</tr>
<tr>
<td>Atonic seizure</td>
<td>Sleep, *cataplexy</td>
</tr>
<tr>
<td>Tonic Seizure</td>
<td>Paroxysmal dyskinesia, *hyperekplexia, *breath-holding attack, paroxysmal extreme pain disorder, *confused arousals, self stimulatory type behavior</td>
</tr>
<tr>
<td>Epileptic spasms</td>
<td>Benign sleep myoclonus, *infantile colic</td>
</tr>
<tr>
<td>Partial-tract seizures</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>Migraine, *papic attack, crescendo ischemic attack (with aphasia), pharmacological attack, neurology with automatisms, *non-ictal confusional states, sleep-related auditory hallucination</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Migraine aura, *Charcot-Bonnet phenomenon, *Hypogeic hallucinations</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>Paroxysmal despotic attack, *pseudoseizure, *syncope, *paroxysmal dyskinesia</td>
</tr>
</tbody>
</table>

*Paroxysmal epileptic seizures are sometimes due to non-epileptic seizures.
**Common epileptic seizure types and some non-epileptic variants.

Compton DE, Berkovic SF. Lancet Neurol 2009;8:370-381

Prolong EEG capturing sleep

Electroclinical Syndrome: Rolandic Epilepsy with Centrotemporal Spikes

- 3-13 years
- A typical attack involves twitching, numbness, or tingling of the child's face or tongue which often interferes with speech and may cause drooling. Secondarily generalized seizures are common.

AED's and Abbreviations

<table>
<thead>
<tr>
<th>AED</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>CGB</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>CPZ</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>DZP</td>
<td>Diazepam</td>
</tr>
<tr>
<td>ESM</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>FBM</td>
<td>Felbamate</td>
</tr>
<tr>
<td>GBP</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>PB</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>PHT</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>RFM</td>
<td>Rufinamide</td>
</tr>
<tr>
<td>TGB</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>TPM</td>
<td>Topiramate</td>
</tr>
<tr>
<td>VPA</td>
<td>Valproate</td>
</tr>
<tr>
<td>VBG</td>
<td>Vigabatrins</td>
</tr>
<tr>
<td>ZNS</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

CGR = Ocarbazepine

LCS = Lamotrigine

LEV = Levetiracetam

LTFM = Rufinamide

Corticosteroids

TGB = Tiagabine

TPM = Topiramate

VPA = Valproate

VEG = Vigabatrins

ZNS = Zonisamide
How do we choose the correct AED?

1. Randomized Clinical Trials:
   - Variation in study design and number of subjects
   - Hypothesis: Superiority, equivalence, non-superiority
   - Outcome: Efficacy versus effectiveness
2. AAN/AES Efficacy and tolerability of the new antiepileptic drugs
   - Evidence: prospective, random, controlled trial
3. ILAE classification Criteria
   - Class I: Randomized controlled trial, Outcome, Treatment duration, Design, superiority, study exit, Appropriate statistical analysis.

References:

Initial treatment of epilepsy

Choices:
Seizure type and Epilepsy Syndrome (Wheless JW, Clarke DF et al. 2007)
Age specific toxicity – VPA hepatotoxicity in children under 2 years
Overall Health – Decrease appetite with topiramate
Learning and Behavior
Phenobarbital and neurocognitive performance (Park J, Yum HS et al. Epilepsy and Behavior, 2013)
Comorbidities (Dunn DW et al. Psychiatry et al. 1999;53(suppl 2):S17-23)
Depression
Hyperactivity or inattentiveness
Migraine
Symptoms of ASD
Sleepiness
Insomnia

Other Considerations (Child specific)

Formulation (Age, Developmental/Neurocognitive status, taste):
- Tablet, Chewable or Wafer, Capsule, Liquid/Suspension, Sprinkles, Injection (ACTH), PR (Rectal diazepam)
Route of Administration:
- Oral
- G-tube
Is the patient on the Ketogenic Diet: Low carbohydrate formulations – crushed tablet
Compliance: Dosing times (Around parent’s jobs, school, sleep/wake schedule)

Common Seizure types, Epilepsy Syndromes and or Constellations

Neonatal seizures
Infantile spasms
Focal (Partial seizures)
- BECTS (rolandic epilepsy)
- Generalized tonic-clonic
- Lennox-Gastaut syndrome
- Absence epilepsy (CAE, JAE)
- Juvenile myoclonic epilepsy
Atypical, Syndrome Specific Management
- Dravet Syndrome and other Progressive Myoclonic Epilepsies, LKS, ESES,
- Febrile convulsions
Neonatal Seizures
Enhanced network excitability/
Lack of maturation of cortical circuits
   a) Focal seizures
   b) Migrating or multi-focal seizures
   c) GTC are rare in neonates

Epilepsy after neonatal seizures.
   a) 22% within 12 months
   b) 33.8% within 48 months

Phenobarbital and Phenytoin the
Traditional AED’s of choice.
Both less than 50% efficacy.

Infantile Spasms
• AAN Practice Guidelines1
  • ACTH probably effective for short term treatment
  • Vigabatrin was found to be possibly effective for short term therapy
  • Superiority of Vigabatrin in Tuberous Sclerosis could not be substantiated

Infantile Spasms Working Group2:
  • ACTH is effective as first-line therapy for IL.
  • Insufficient evidence to define precisely the optimum ACTH dose and duration of treatment for IL.
  • VGB as a first-line treatment option (6-9 months because of constriction of visual fields)

Infantile Spasms
The United Kingdom Infantile Spasms Study (UKISS)3 – outcome to 14 months: A multicenter RCT (VGB vs. Hormonal therapy):
  • Better efficacy with hormonal therapy initially but no difference at 14 months
  • Neurocognitive outcome better.

Other AED’s used in Neonatal Seizures
Animal studies suggest Topiramate may be anticonvulsant and neuro-protective4
   Anecdotal evidence for its use in humans - No suspension or IV preparation

Case series: Levetiracetam, Clonazepam, Midazolam,
   Lidocaine, Paraldehyde, Carbamazepine, Valproic Acid,
   Primidone, Vigabatrin

Expert consensus: PHT, PB, IV benzodiazepine2

West Syndrome (Infantile spasms)
• clusters of repetitive flexor spasms (salams)>extensor spasms, head nods
• 15% to 30% unknown etiology (cryptogenic) Tuberous Sclerosis or any brain abnormality
• EEG: Hypsarrhythmia, high voltage slowing with chaotic multifocal spike wave, electodecremental seizures

Other agents: VPA, Nitrazepam, Topiramate, Zonisamide, Pyridoxine
Ketogenic Diet: Few cases of initial therapy but possibly effective2
FDA approval: ACTH, Vigabatrin
Focal Seizures

- 25 RCTs and 1 meta-analysis\(^1\)
  - 2 (OXC, PHT) had class 1 evidence, 1 study demonstrated differential effectiveness (OXC)
- Level A, B: Oxcarbazepine; Level C: CBZ, PB, PHT, TPM, VPA
- AAN/AES Efficacy and tolerability of the new antiepileptic drugs\(^2\): Monotherapy - GBP, LTG, TPM, OXK
- SIGN\(^3\) & NICE\(^3\): In addition to the agents above - LEV, VGB, CLB, LCS, TGB, ZNS


Rolandic Epilepsy with Centroltemporal Spikes

- ILAE treatment guidelines\(^1\)
  - Level A,B – None
  - Level C: CBZ, VPA

- RCT: Sulthiame, Gabapentin\(^2\)

- NICE\(^3\): CBZ, LTG, LEV, VPA, OXK, CLB, GBP, TPM

2. Ogure H. Brain Dev. 2011;33:207-212

Generalized Epilepsy Syndromes

Absence - Childhood (CAE) and/or Juvenile (JAE)

1. ILAE treatment guidelines\(^3\)
   - Level A: ESM, VPA, LTG
2. SIGN\(^2\), NICE\(^3\): VPA, ESM, LTG
3. Expert Consensus Europe and USA\(^4\): VPA, ESM, LTG
4. PHT, CBZ, GBP, VGB, TGB, 7OCD – may exacerbate the condition


Recommendation for Focal Seizures

USA\(^1\)

- Mono: CBZ, VPA, PB, TPM, OXK
- Poly: CBZ, VPA, LTG, LEV, TGB, ZNS

Europe\(^2\)

- Minimal: PHT, VPA, PB, TPM, OXK
- Moderate: CBZ, VPA, PB, TPM, OXK
- Seizure control: CBZ, VPA, LTG, LEV, TGB, ZNS


Medication recommendation for Benign Rolandic Epilepsy

Expert consensus in the US\(^1\):
- OXZ and CBZ usually appropriate
- LTG, LEV, GBP sometimes appropriate

Expert Consensus in Europe\(^2\):
- VPA usually appropriate
- CBZ sometimes appropriate

Is treatment Necessary?\(^3\) – 43 treated and 36 not treated patients had the same seizure outcome.


Juvenile Myoclonic Epilepsy (myoclonic Epilepsy of Janz Impulsive petit mal, jerk Epilepsy)

- Most cases occur between 12 and 18 years
- Seizure types:
  - Myoclonic seizures (100%)
  - GTc (approx. 90%)
  - Absence (10-30%)
- Triggers: Lack of Sleep, Fatigue, Alcohol
- VPA historical drug of choice\(^1\) (side effect profile my negate its use)

Juvenile Myoclonic Epilepsy (Epilepsy with Grand Mal on Awakening)

1. ILAE treatment guidelines\(^1\)
   - No level A, B or C evidence
   - Class 4 studies: Concomitant, LTG, LEV, TPM, VPA, ZNS
2. SIGN\(^2\): VPA, LTG, TPM
3. NICE\(^3\): VPA, LTG, TPM, LTG
4. Expert Consensus Europe and US\(^4\): VPA (male), LTG (female), LEV (Europe) – TPM, ZNS, CLB usually appropriate.
5. PHT, CBZ, GBP, VGB, TGB, DIX – may exacerbate the condition

Lennox-Gastaut Syndrome

- EEG: Slow spike and wave
- 1-4% of patients with childhood epilepsy but 10% of epilepsy when younger than 5 years.
- Seizures often pharmacoresistant: tonic, atonic, myoclonic, GTC, atypical absence
- VPA historical drug of choice

Syndromes associated with neurocognitive deficits, language impairment and continuous epileptiform activity during sleep:
1. Landau-Kleffner Syndrome
2. Syndrome of Continuous Spike and Wave Activity in Sleep
3. Malignant Rolandic Epilepsy

Diagnosis:
1. History
2. Prolonged EEG capturing NREM sleep is required for the diagnosis

Initial medications of choice - High Dose Diazepam (0.5-1mg/kg\(^1\)) VPA, Corticosteroids, ACTH, IVIG

Lennox-Gastaut Syndrome

1. ILAE treatment guidelines - Not reviewed
2. Felbamate was the first to show efficacy\(^1\)
   - Side effects and organ toxicity negate or limit its use.
3. SIGN\(^2\): VPA, LTG, TPM, CLB, FBM, RFM
4. NICE\(^3\): VPA, LTG, RFM, TPM
5. US Expert Consensus - usually appropriate: VPA, TPM, LTG; Sometimes appropriate ZNS
6. Europe Usually Appropriate – VPA; Sometimes LTG, TPM, CLB, ETM

3. Scottish Intercollegiate Guidelines. ePrints www.sign.ac.uk/guidelines/77/overview/index

1. ILAE treatment guidelines, NICE, SIGN, Expert Opinion - Not reviewed
2. Case reports: VPA, diazepam, ETH, CLB, CZP
   - Less cases described using: LTG, STM, FBM, VGB, LEV and the ketogenic diet.
   - High-dose vigabatrin therapy
   - Combination therapy of VPA and ethosuximide
   - Short cycles of high-dose diazepam (oral or PR DPH, 0.5-1 mg/kg per day for 6-7 days)
   - Intramuscular synthetic ACTH-Z therapy (0.01-0.04 mg/kg per day for 11–43 days).

Dravet Syndrome and other Progressive Epilepsy Syndromes associated with myoclonic, atonic and other generalized or mixed seizure types

- Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy):
   - Prolong febrile seizure
   - Triggers – photic stimulation, exogenous body heat, eye closure and fixation on patterns.
   - Multiple seizure types – Myoclonus is often prominent.
- Progressive Myoclonic Epilepsy:
  - Severe Myoclonus
  - Generalized Seizure types predominately but focal seizures may be seen
  - Progressive Course including Neurocognitive regression and cerebellar manifestations +/- visual and hearing impairment
• Dravet Syndrome\textsuperscript{1}: Valproate, benzodiazepine is used as an abortive agent
  – Topiramate, levetiracetam, bromide, and the ketogenic diet
• Stiripentol (modulator of GABA A receptor) – proved efficacy in two independent randomized placebo-controlled trials, when combined with valproate (71% > 50% reduction versus 5% in placebo group) and clobazam
• PMEs\textsuperscript{2}: ZNS, Piracetam, LEV, CZP, VPA.
• Historically, both alcohol and N-acetylcysteine have been helpful in some patients with PMEs.


Common Seizure types, Epilepsy Syndromes and or Constellations

<table>
<thead>
<tr>
<th>Seizure types</th>
<th>Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Seizures</td>
<td>Phenobarbital (LEV, TPM)</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>ACTH, Vigabatrin</td>
</tr>
<tr>
<td>Focal (Partial seizures)</td>
<td>Ocarbazepine, Carbamazepine</td>
</tr>
<tr>
<td>Rolandic Epilepsy</td>
<td>Ocarbazepine, Carbamazepine, GBR, STM</td>
</tr>
<tr>
<td>Absence epilepsy (CAE, JME)</td>
<td>Ethosuximide, Valproic Acid, LTG</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Lamotrigine (L), Valproic Acid (M)</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>Valproic Acid, Lamotrigine, TPM, FLB</td>
</tr>
<tr>
<td>Atypical, syndrome Specific Management</td>
<td></td>
</tr>
<tr>
<td>Dravet syndrome and other Progressive Myoclonic Epilepsies</td>
<td>Stiripental (D), Valproic Acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific Management</th>
<th>LKS, ESES</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose diazepam, Valproic Acid, Corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

• Many Pediatric Epilepsy Syndromes were not covered and have not been adequately studied (more studies are required).
  - Neuronal Ceroid Lipofuscinosis (PPT1, TPP1, CTSL)…large occipital spikes to low frequency photic (Green, 1971)
  - Alpers Syndrome (POLG-related disorders)…1-3/sec spike and wave with focal motor activity (Brick, 1984)
  - Neuronal Ceroid Lipofuscinosis (PPT1, TPP1, CTSL)…large occipital spikes to low frequency photic
  - Sialidosis Type 1 (NEU1)…posterior spikes over vertex (Engel, 1977)
  - Retts Syndrome (MECP2, CDKL5)…central spike with contralateral touch (Robertson 1978)
  - Lissencephaly (ARX, LIS1)…high voltage delta and theta frequency with admixed delta

• Future Hope – We may be able to (based on Genetics, EEG, Signs and symptoms) choose case or Epilepsy Syndrome specific management.

New Onset of Epilepsy in the Elderly
December 6, 2013

Ilo E. Leppik, MD
Professor of Neurology and Pharmacy
University of Minnesota

Learning Objectives

• Appreciate complexities of choosing the optimal AED
• Learn about proper use of therapeutic drug monitoring in the elderly
• Understand the importance of life situations on the quality of life

Impact on Clinical Care and Practice

• Deciding if to treat after a single seizure
• Choosing the best AED for elderly
• Best use of AED monitoring

The Elderly with Epilepsy

• Community dwelling
• Nursing home
• Hospital intensive care unit

Disclosure

During my almost 40 years in this field, I have received honoraria, consulting fees and or research grants from almost all companies developing or manufacturing drugs and devices related to epilepsy. The majority of my research funding has come from the NIH or other federal sources.

My current commitments are: chairing the data and safety committee for the Medtronic deep brain stimulator and consulting with Eisai. Upsher Smith, UCB and Lundbeck.
Defining Epilepsy

- Classical: Two or more unprovoked seizures
- Could a single seizure in the context of a CNS disorder be diagnosed as epilepsy?
  - Debate at AES 2007*
- A diagnostic must be assigned to prescriptions
  - 345.xx (epilepsy) or 780.39 (convulsion)
- Who makes the diagnosis in elderly?
  - Very few neurologists involved
- A seizure may not be epilepsy
  - Cardiac, Metabolic, Respiratory, Drugs/alcohol, Infections


Etiology of Epilepsy, Age 65+

- Cryptogenic: 51%
- Stroke: 38%
- Degenerative: 12%
- Tumor: 5%
- Trauma: 2%
- Infection: 2%

Seizures in Alzheimer’s

- Clinically apparent (mostly convulsive) seizures in Alzheimer’s
  - 7% to 21% of persons with sporadic AD have at least one unprovoked seizure.
  - Seizure incidence increases in earlier onset AD*
  - Risk ratio = 87 if onset 50-59
  - Risk ratio = 3 if onset 70-79 years of age

*Amatniek et al. Epilepsia 2006; 47:867-872.

Incidence of Epilepsy in US Nursing Homes*

- US Medicare data base of 8 million plus subjects.
- Entry = No epilepsy on admission; 1-3 year of follow-up.
- 3,613,926 NH residents followed forward
- Overall = 1,642 / 100KPY (10 fold higher than outpatients)
- Stroke = 2,762 / 100KPY
- Head injury = 4,566 / 100KPY
- Parkinson’s Disease = 1,766 / 100KPY
- Dementia (any type) = 1,644 / 100KPY
- No predisposing diagnoses, 1,245/100KPY

Prevalence (cases at a point in time)

- In Community higher as older *
  - 1.8% identified as having epilepsy by having an ICD-9-CM code representative of this condition.*
- In nursing homes, lower as older**
  - Overall 6% to 10% by ICD-9 codes 345.xx or 780.3
  - 16.4% in 65-74; 8.3% in 75-84; 3.7% in 85+
- In intensive care units***
  - 30% of patients following cardiorespiratory arrest.
  - 1% to 21% with intracerebral hemorrhage.

Seizure Types

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTC</td>
<td>27.1%</td>
</tr>
<tr>
<td>CPS</td>
<td>38.3%</td>
</tr>
<tr>
<td>Mixed Partial</td>
<td>14.3%</td>
</tr>
<tr>
<td>GTC &amp; Partial</td>
<td>7.5%</td>
</tr>
<tr>
<td>SPS</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

Co-morbidities-medical

- Incidence and severity of these are unknown
  - Depression
  - Anxiety
  - Visual impairment
  - Osteoporosis
  - Memory loss
  - Other medical disorders

Geriatric Epilepsy Management

First Seizure in Elderly: To treat or not to treat, that is the question

- Reasons to treat
  - Prevent another seizure
  - What is the risk of 2nd seizure
    - After a stroke in Alzheimer’s, etc?
    - Unknown etiology?
- Reason not to treat
  - Cognitive side-effects
  - Increasing falls and fractures

Social Issues

- Loss of driving privileges
- Lack of spousal support
- Emotional shock of developing epilepsy
- Cost of medication
- Fear of seizures, falling, embarrassment
- Adult children of parents (role reversal from pediatric practice)
"First" seizure in Elderly

- Prospective observational study of adults seen by a hospital-based first seizure service between 2000 and 2011.
- The likelihood of a second seizure at one year was 53% (95% CI 45-62) in older patients and 48% (95% CI 44-51) in younger patients.
- Independent predictors of seizure recurrence were:
  - remote symptomatic etiology.
  - first seizure arising from sleep.
  - epileptiform abnormality on EEG.
  - partial seizures.
  - not age.


2nd seizure after "1st" seizure: stroke

- 159 patients
  - Early-onset seizures occurred in 57 patients
  - late-onset (>14 days post-stroke) in 102 patients
- 68 (43%) with "1st" seizure had recurrence
- Risk factors for more seizures
  - Late onset "1st" seizure (p=0.01)
  - Hemorrhagic component
  - Occipital involvement
  - Low Rankin score after "1st" seizure

Studies of Other AEDs in Elderly

- LEV vs CBZ, 128 patients, prospective, 1 year*
  - no significant difference in number of seizure-free patients between LEV and CBZ (p = 0.08);
  - LEV caused significantly fewer (p = 0.02) side effects than CBZ.
  - attention deficit, frontal executive functions and functional skills were significantly worse in the CBZ group.
- Lamotrigine vs CBZ, double-blind, newly diagnosed 125 eligible subjects**
  - A borderline difference in the IADL symptom subscales favored lamotrigine.
- Lamotrigine vs CBZ, double-blind, newly diagnosed 125 eligible subjects***
  - a borderline difference in the IADL symptom subscales favored lamotrigine.


WHICH AED?

Ideal Properties of an AED for Elderly

- Efficacy
- Safety
- No drug interactions
- Good bioavailability
- Linear elimination kinetics
- Wide therapeutic index

Ideal AED for patient: The one that works

Summary of Properties

<table>
<thead>
<tr>
<th>AED</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Broad Spectrum</th>
<th>No relevant interactions</th>
<th>Renal Emocion</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>(X)</td>
</tr>
<tr>
<td>PHT</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>VPA</td>
<td>X</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>ZNS</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

GBP, LTG, CBZ in Elderly*

- 18-center randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures.
- Patients were randomly assigned to one of three treatment groups:
  - GBP 1,500 mg/day,
  - LTG 150 mg/day
  - CBZ 600 mg/day
- Early terminations:
  - LTG 44.2%, GBP 51%
  - CBZ 64.5% (p = 0.0002)
- Seizure control was similar among groups.
- LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

Evidence for choosing among AEDs in elderly

- There is some evidence for superiority of newer AEDs over CBZ
- No comparisons for phenytoin vs newer AEDs
- My opinion:
  - Avoid AEDs with significant drug interactions
  - Elderly healthy are like women of childbearing potential—may have new medical conditions next visit.
  - Avoid AEDs that are highly protein bound
  - Favor AEDs with long half-lives
  - Favor AEDs with suspension, sprinkle or IV formulations

Polypharmacy in the Elderly

- All elderly are treated with polypharmacy, but only one of them is an AED.
- Many studies have been done about AED-AED interactions, - But very few about AED-other drugs

Effect of Enzyme-Inducing AEDs

<table>
<thead>
<tr>
<th>Non-AEDs</th>
<th>Plasma Level Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>50%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>??? – 3A4S metabolism</td>
</tr>
<tr>
<td>Ca-channel blockers</td>
<td>30%–93%</td>
</tr>
<tr>
<td>Statins</td>
<td>50%–80%</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>27%–31%</td>
</tr>
</tbody>
</table>

Effect of CBZ on Serum Simvastatin

- 2 subjects

Age-related changes affecting PK and TDM

- Pharmacokinetics (PK)
  - Absorption
    - Gastric pH
    - GI transit time
  - Elimination
    - Hepatic
    - Renal
- Therapeutic Drug Monitoring (TDM)
  - Protein binding
    - Of AED
    - Of other drugs

Indications for Therapeutic Drug Monitoring*

- When therapeutic goal has been reached
  - At least 4 half-lives beyond dose change
- Side-effects
- Breakthrough seizure
- Co-medications added or removed
- Change in health status
- Monitor compliance


Case report: The woman who inspired me

- 76 year old woman from northern Minnesota
- Developed complex partial seizures, poorly controlled
- Local MD prescribed phenytoin and valproate
- Developed “Alzheimer’s” and Parkinson’s
- Total AED levels “normal range”
- Sent to MINCEP last stop before NH
- Unbound levels high
- Lived for 18 more years after adjustment of AEDs enjoying independent life.
- Into NH because of lack of caregivers and arthritis
- We traded copies of our books; she wrote it in NH because she did not want to partake in activities with the old people!
- Lived to 94 years of age

The woman who inspired me 2 decades ago

TDM Caveats

- Usual laboratory values are inappropriate
  - Abnormal protein binding
  - Elderly may need lower concentrations for efficacy
  - May have side-effects more readily
- Unbound (free) levels needed for AEDs that have binding greater than 70%
- Monitoring of drugs other than AEDs should be done (but is rarely performed)
- Usual fluctuations in compliant outpatients is less than 20%, but levels in some NH patients “bounce” more than 200%.

Conclusions

- Epilepsy is common in elderly
- Elderly have many co-morbidities
- Although there is little evidence for it, the first seizure in elderly often leads to treatment
- Because of drug interactions of AEDs with other drugs, those AEDs with few interactions are preferred
- TDM is important but “laboratory ranges” may not be appropriate.
- Much more research needs to be done in elderly.
Choosing the right dose is important
Use TDM to guide.
Prognosis for New-Onset Epilepsy
Dec. 6th, 2013

Scott Mintzer, MD
Jefferson Comprehensive Epilepsy Center
Thomas Jefferson University
Philadelphia, PA

Learning Objectives
• To understand the prognosis for long-term seizure control in new-onset epilepsy and specific epilepsy syndromes
• To review the evidence for the question of whether epilepsy prognosis is drug-specific

Seizure outcome prognosis
1) Overall epilepsy population
2) By syndrome
3) Course
4) Predictors
5) Is response/prognosis drug-dependent?

The magic number: 68%
• Brodie et al 2012: 68% terminal (1-year) remission
• Cockerell et al 1997: 68% in 3-year remission
• Lindsten et al 2001 (adults): 68% 1-year remission
  (64% 3-year)
• Silangi & Schmidt 2006 (kids): 67% terminal (5-year) remission

What kind of prognosis?
• Seizure outcome
• Treatment outcome (including side effects)
• Social function
• Occupational function
• Mortality

Disclosure
Name of Commercial Interest
Upsher-Smith, Eisai, Acora, UCB, Lundbeck, Pfizer

Type of Financial Relationship
Consultation/advisory board member
Prognosis for primary generalized epilepsy

- Pediatric setting: 94% seizure-free (Silanpää & Schmidt 2008)
- Adult/adolescent setting: 64% seizure-free (Mohanrak & Brodie 2007)
- Adult/adolescent setting: 76% seizure-free (Kharazmi et al 2010)

Specific syndromes: CAE

7-year remission measured in all studies

75% seizure-free for 2 years (Janz 1985)

Specific syndromes: JAE

2-year remission measured in all studies

75% seizure-free for 2 years (Janz 1985)

9% of patients successfully weaned off AEDs

68% seizure-free for 5 years (Geithner et al 2012)

19% successfully weaned off AEDs

67% with “benign” course (Bakyan et al 2008)

19% successfully weaned off AEDs

19% with “benign” course (Bakyan et al 2008)

19% with “benign” course (Bakyan et al 2008)

Variation by syndrome (LGS, myoclonic-astatic, West syndrome), but numbers for each are small

Better overall for myoclonic-astatic and for non-syndromic SGE

Prognosis for symptomatic generalized epilepsy in kids

42% attained a 2-year remission (Berg et al 2001)

2/14 (14%) attained a 5-year remission (Silanpaa & Schmidt 2006)

28% with SGE attained 5 years of remission (Camfield x2 2007)

24% died

Variation by syndrome (LGS, myoclonic-astatic, West syndrome), but numbers for each are small

Better overall for myoclonic-astatic and for non-syndromic SGE

Prognosis for focal epilepsy syndromes

42% in remission with Rx (Stephen et al 2001)

MTS: 25% had 1-year remission with Rx (W-J Kim et al 1999)

Cryptogenic focal epilepsy: 23% with terminal 5-year remission (Gasparini et al 2013)
Long-term course of epilepsy

- Early remission - within the first 6-12 months of Rx
- Delayed remission - ≥ 6 - 12 months from Rx
- Relapsing-remitting course - recurrent seizure following a period of seizure-freedom
- Resistant - never a period of sustained seizure-freedom (1 - 5 years)

Studies of long-term course

<table>
<thead>
<tr>
<th>Course</th>
<th>early remission</th>
<th>late remission</th>
<th>relapsing/remitting</th>
<th>resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silanpää &amp; Schmidt 2006 (n=144)</td>
<td>31%</td>
<td>32%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Brodie et al 2012 (n=1098)</td>
<td>37%</td>
<td>22%</td>
<td>16%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Predictors: age and # of seizures

- Bonnet et al 2012

Predictors: # of drug failed

- Brodie et al 2012
- Schiller and Najjar 2008

Other prediction studies

- Gender?
  - Brodie et al 2012: best outcome in 42% of men, 31% of women
- Age
  - Found NOT to predict outcome in multiple studies, contradicting SANAD
- Partial seizures
  - Worse prognosis than for generalized tonic-clonic seizures
  - Diametric opposite of the surgical literature in resistant patients!

Predictors in kids (Berg et al 2001)

- Good
  - Idiopathic generalized epilepsy
  - Onset ages 5 - 9 years
- Bad
  - Remote symptomatic etiology
  - Family history
  - Higher initial seizure frequency (≥1/month)
  - Focal slowing on EEG
  - Seizure frequency confirmed as prognostic sign in other studies
  - Others have been inconsistently found
Adult new-onset partial epilepsy trials -

Serial AED efficacy: seizure-free rates in resistant patients

Deficiencies in efficacy literature

Methods: case patients
Methods: controls

- 2 controls matched to each case by consecutive retrospective chart review
- First two patients meeting these criteria:
  a. Office visit within 30 days of the case patient (index date)
  b. Same seizure status as the case prior to the index date
  c. On a single AED which was not changed at the index date
  d. Seizure outcome available 6 months after the index date
- Baseline differences in # of AEDs failed between cases and controls required statistical adjustment

Results: 6 month seizure outcome

<table>
<thead>
<tr>
<th>Status at index date</th>
<th>Group</th>
<th>N</th>
<th>Seizure-free after index date</th>
<th>Recurrent seizures after index date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure-Free</td>
<td>controls</td>
<td>23</td>
<td>78.3%</td>
<td>21.7%</td>
</tr>
<tr>
<td></td>
<td>switched</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>same Rx</td>
<td>46</td>
<td>95.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Non Seizure-Free</td>
<td>cases</td>
<td>20</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>switched</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>same Rx</td>
<td>40</td>
<td>20%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Multivariate analysis of 6-month outcome

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free patients, controls vs. cases</td>
<td>8.53</td>
<td>1.02 - 61.19</td>
<td><strong>0.06</strong></td>
</tr>
<tr>
<td>Seizure-free patients, per previous AED failure</td>
<td>0.85</td>
<td>0.57 - 1.39</td>
<td>0.47</td>
</tr>
<tr>
<td>Non-seizure-free patients, controls vs. cases</td>
<td>1.66</td>
<td>0.36 - 8.42</td>
<td>0.52</td>
</tr>
<tr>
<td>Non-seizure-free patients, per previous AED failure</td>
<td>0.61</td>
<td>0.37 - 0.91</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>

Summary

- Two-thirds of patients with epilepsy in remission at any given time
- 15-20% of patients have a relapsing-remitting course
- About half of these are in remission at any given time
- CAE and BRE patients do better
- JAE, SGE, and MTS do worse
- View that SGE and MTS can rarely be medically controlled is incorrect

Summary (cont.)

- Major predictors are # of seizures at time of Rx and # of drugs failed
- However, "success" of serial drug trials likely due to spontaneous remissions
- Good prognosis may, in about 1/6 of patients, be drug-dependent
- Extent of overlap of the spectra of AEDs remains to be determined
Conclusions: 
Treating Patients with New Onset Epilepsy

Gregory Krauss, MD  
Professor of Neurology  
Johns Hopkins University

Disclosure

Eisai, UCB Pharma, Sunovian, SK Bios, NINDS, Upsher Smith: Investigator  
Eisai, UCB Pharma: Consultant via JHU  
Lundbeck: SHARE vision safety board

Questions:

Treating Patients with New Onset Epilepsy  
- Population Study of First Seizures & Need for Treatment  
- Berndt Pohlmann-Eden, MD, PhD  
- Drug Choices in New-Onset Epilepsy  
- Tracy A. Glauser, MD  
- New-Onset Epilepsy in Children  
- Dave F. Clarke, MBBS  
- New Onset Epilepsy in the Elderly  
- Ilo Leppek, MD  
- Treatment Prognosis for New-Onset Epilepsy  
- Scott Mintow, MD  
- Conclusion & Audience Discussion

Treating Patients with New Onset Epilepsy

Thank you!

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