Antiepileptic Therapy Symposium: One Size Does Not Fit All: Personalized Medical Care

Symposium Co-Chairs:

Aristea Galanopoulou, M.D., Ph.D., and

Angus A. Wilfong, M.D.

Saturday, December 7, 2013
Convention Center – Ballroom B, Level Three
5:15 p.m. – 8:00 p.m.
OVERVIEW
The selection of the optimal therapy for a patient with seizures or epilepsy depends not only upon the specific epilepsy type but also upon a variety of individual characteristics of the patient. The goal of this AET symposium will be to discuss some of these factors and present treatment algorithms that would allow for more personalized medical care for patients with seizures and maximize the efficacy and tolerability of the selected treatments. Specifically, this symposium will discuss how to use genetic tests to select appropriate therapies, select appropriate drug delivery methods to best serve each patient’s needs, recognize and treat early allergic reactions to anti-seizure drugs as well as prevent cross-allergies with other drugs, select the optimal therapies for women with epilepsy to prevent teratogenic or other adverse effects on their reproductive system, and optimize epilepsy therapies in patients with HIV. A discussion of the future perspectives to overcome current barriers in AET implementation will also be presented.

LEARNING OBJECTIVES
- Develop an algorithmic approach for the selection of optimal antiepileptic therapy for each individual patient
- Develop an algorithmic approach for the selection of the optimal antiepileptic formulation and delivery system for each individual patient with resulting increased adherence
- Recognize early adverse drug reactions and the patient populations at risk for developing them and implement treatment protocols that minimize such adverse outcomes.

TARGET AUDIENCE
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, “mid-level” providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

PROGRAM
5:15 – 5:30 pm Award: J. Kiffin Penry Award Presentation
5:30 – 5:45 pm Introduction
Aristea Galanopoulou, M.D., Ph.D.
5:45 – 6:10 pm Genomic Approaches in Selecting AETs: Current State
Norman Delanty, M.D.
6:10 – 6:35 pm Personalizing Drug Delivery
Emilio Perucca, M.D., Ph.D.
6:35 – 7:00 pm Management of Allergic Reactions to AETs
Bernard Cohen, M.D.
7:00 – 7:25 pm Women Issues in AET Implementation
Page B. Pennell, M.D.
7:25 – 7:50 pm Management of Seizures in HIV Patients
Gretchen L. Birbeck, M.D., M.P.H.
7:50 – 8:00 pm Conclusions
Angus A. Wilfong, 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 2.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
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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](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 0073-9999-13-088-L01-P and provides 2.5 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 Antiepileptic Therapy 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: Practice-Based Learning, Comprehensive Patient Care and Communication Skills

**ACKNOWLEDGEMENT**
This program is supported in part by an educational grant from Eisai Inc., Sunovion Pharmaceuticals Inc., and UCB, 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**

**Gretchen Birbeck, M.D., M.P.H.**
Gretchen Birbeck is a neuroepidemiologist whose clinical and research focus is on epilepsy in sub-Saharan Africa. She is the principal investigator for an ongoing cohort study of new onset seizure among HIV positive adults in Zambia. She is also conducting a clinical trial of enteral levetiracetam for seizure control in pediatric cerebral malaria in Malawi. In August, she joined Epilepsy Division within the University of Rochester's Department of Neurology.

Gretchen Birbeck, M.D., M.P.H. discloses receiving support as Federal/State/Not-for Profit Funding from NIH and the Dana Foundation.

**Bernard Cohen, M.D.**
Bernard A. Cohen, MD is Professor of Pediatrics and Dermatology at the Johns Hopkins University School of Medicine. He is boarded in Pediatrics, Dermatology, and Johns Hopkins University School of Medicine. He is boarded in Pediatrics, Dermatology, and Pediatric Dermatology. Dr. Cohen practices pediatric dermatology at the Johns Hopkins Children's Center where he is often called upon to evaluate children and young adults with cutaneous drug reactions. The the multidisciplinary faculty at the pediatric burn unit in the new children's hospital are experienced in evaluating and managing patients with severe drug reactions.

Bernard Cohen, M.D. discloses receiving support as Consulting/Advisory Board Activity from Sanofi Aventis consultation for Head lice.

**Norman Delanty, M.D., FRCPI**
Prof. Norman Delanty is Consultant Neurologist and Director of the Epilepsy Service and National Epilepsy Surgery Programme at Beaumont Hospital, Dublin. He is also Honorary Associate Professor at the Department of Medicine, Royal College of Surgeons in Ireland. He initiated the epilepsy genomics programme in Dublin, and collaborates internationally. In 2009, Prof. Delanty was awarded the ILAE International Ambassador for Epilepsy Award presented at the International Epilepsy Congress in Budapest. He is now President of the Irish Chapter of the International League Against Epilepsy. His goal is to establish a comprehensive stand-alone National Epilepsy Center in Ireland.

Norman Delanty, M.D., FRCPI discloses receiving support as Consulting/Advisory Board Activity from UCB Pharma Eisai Lundbeck; as Honoraria from Commercial Sources from GSK.

**Aristea Galanopoulou, M.D., Ph.D. (Co-Chair)**
Aristea Galanopoulou is currently an Associate Professor of Neurology and Neuroscience at the Albert Einstein College of Medicine in Bronx NY. Dr Galanopoulou completed her medical training at the Medical School of Athens, Greece, her PhD at McGill University in Canada, and the adult Neurology and Clinical Neurophysiology training at the Albert Einstein College of Medicine. Dr Galanopoulou has been studying the impact of neonatal status epilepticus in brain development and the role of GABAA receptor signaling in this process, as well as the pathogenesis and treatment of infantile spasms using animal models.

Aristea Galanopoulou, M.D., Ph.D. discloses receiving support as Consulting/Advisory Board Activity from Viropharma (consulting honorarium); as Royalties/Income from Patents from Morgan & Claypool
Page Pennell, M.D.
Page Pennell, MD, is an adult epileptologist and Director of Epilepsy Research at Brigham and Women's Hospital, Harvard Medical School. She is an expert in maternal-fetal health in epilepsy, and pharmacokinetics of AEDs during pregnancy. She currently serves on the AES Board of Directors, the Epilepsy Research Foundation Scientific Advisory Board, and the Epilepsy Foundation's Professional Advisory Board. Her actively enrolling multi-center, clinical research protocols include prospective, observational studies of fertility, hormones, seizures control, and AED changes in women with epilepsy from preconception through postpartum, funded by the Epilepsy Foundation and NIH (NINDS and NICHD).

Page Pennell, M.D. discloses receiving support as Federal/State/Not-for Profit Funding from 1) NINDS UO1, MONEAD; 2) NINDS RO3, Neurosteroids during pregnancy in epilepsy; 3) ETP/EF for WEPOD study; as Participation in Foundation or Not-for-Profit Organizations from volunteer member of EF PAB and AES BOD.

Emilio Perucca, M.D., Ph.D.
Dr. Perucca trained as a clinical pharmacologist and neurologist in London, UK. He is Professor at the University of Pavia, Italy and Director of the Clinical Trial Center at the local National Neurological Institute. He is President of the International League against Epilepsy and member of the board of Epilepsia, Epileptic Disorders, Epilepsy Research, Seizure, CNS Drugs, Lancet Neurology, and other journals. In 1997 he received the ILAE-IBE Ambassador for Epilepsy Award. His interests relate to the treatment of epilepsy. He co-edited several international textbooks and authored over 400 articles in clinical pharmacology and epilepsy therapy.

Emilio Perucca, M.D., Ph.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Conference speaker fees by Eisai, GSK, UCB and Viropharma.; as Consulting/Advisory Board Activity from GSK, Lundbeck, and Viropharma; as Honoraria from Commercial Sources from Supernus; as Research Funding from For Profit Commercial Sources/Principle Investigator from Vertex; as Federal/State/Not-for Profit Funding from Italian Medicines Agency, italian Ministry of Health; as Participation in Foundation or Not-for-Profit Organizations from President, International League against Epilepsy; Research Coordinator, Institut IDEE, Lyon, France; Director, Clinical trial Center, National Institute of Neurology, Pavia, Italy.

Angus Wilfong, M.D. (Co-Chair)
I am a practicing academic Pediatric Neurologist/Epileptologist and direct the Comprehensive Epilepsy Program at Texas Children's Hospital and am an Associate Professor of Pediatrics and Neurology at Baylor College of Medicine, Houston, Texas. I oversee and direct a team providing care for children with epilepsy that includes medical and surgical therapies and am active in clinical and translational research studies in epilepsy and related disorders.

Angus Wilfong, M.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Eisai - non-branded speaker program Cyberonics - speaker programs Supernus - speaker programs; as Consulting/Advisory Board Activity from Cyberonics - consultancy Lundbeck - consultancy Supernus - consultancy; as Royalties/Income from Patents from Up-To-Date publication royalties; as Research Funding from For Profit Commercial Sources/Principle Investigator from Novartis - PI Eisai - PI UCB - PI Cyberonics - PI Pfizer - PI; as Federal/State/Not-for Profit Funding
from NIH U01 NS045911; as Participation in Foundation or Not-for-Profit Organizations from Epilepsy Foundation of America Hope for Hypothalamic Harmatoma Sturge-Weber Foundation Hemispherectomy Foundation Lennox-Gastaut Foundation.

**Lara Jehi, M.D. (CME Reviewer)**
Dr. Lara Jehi is an adult epileptologist at the Cleveland Clinic Epilepsy Center. She serves as the head of the Outcomes Research Program, and the Director of Research. She also serves as the Associate Program Director of the Clinical Research Unit at Cleveland Clinic within the auspices of the NIH-funded Clinical and Translational Science Collaborative. In these various roles, she has focused on advancing the understanding of the mechanisms of seizure recurrence after epilepsy surgery, and expanding the vision of treatment outcomes in clinical practice.

Lara Jehi, M.D. discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from research funding from UCB pharma to investigate the relationship between interictal EEG findings and epilepsy refractoriness. I get no salary support from this project.; as Participation in Foundation or Not-for-Profit Organizations from board of trustees for cleveland chapter of Epilepsy Association. This is an unpaid contribution (I volunteer my time).

**Shahin Hakimian, M.D. (CME Reviewer)**
Shahin Hakimian, MD is an Assistant Professor of Neurology at Regional Epilepsy Center and University of Washington in Seattle. He is the clinical director of the Harborview EEG/Clinical Neurophysiology Laboratory.

Shahin Hakimian, M.D. discloses receiving support as Consulting/Advisory Board Activity from OptumRx (A drug benefits advisory company); as Federal/State/Not-for-Profit Funding from NIH R01 (HD070973-01A1).

**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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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.
AET Symposium 2013:
One size does not fit all:
Personalized Medical Care
December 7th, 2013

Co-chairs:
Aristea S. Galanopoulou, MD PhD
Albert Einstein College of Medicine, Bronx NY USA
Angus A. Wilfong, MD
Baylor College of Medicine, Houston, TX USA

Disclosure
Name of Commercial Interest                        Type of Financial
Viropharma                                          Relationship
Morgan & Claypool Publishers                        Consulting fees
John Libbey Eurotext                                Book royalties
Research Funding Agencies:
NINDS                                                Research Grant
Autism Speaks                                       Research Grant
CURE                                                 Research Grant
Department of Defense                                Research Grant

American Epilepsy Society | 2013 Annual Meeting

Personalized factors affect
epileptogenesis

Personalized factors affect
treatment response
Questions in AET selection

- **For a specific patient**, can we pre-determine:
  - What is the best medication and treatment protocol?
  - Will(s)he respond to the treatment, for how long?
  - Will(s)he develop adverse effects to a drug and when?
- **For a specific situation, patient, or seizure pattern**, what is the best available drug formulation and delivery routes to optimally manage them (e.g., circadian or cyclic patterns of seizures; rescue medications for acute prolonged seizures).
- Can we recognize early the first signs of an **allergic reaction** and how can we best manage them?
- How do **comorbid or other associated conditions** influence the selection of an AET (e.g., pregnancy, HIV)?

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**Case 1:**
A 20 year old girl of Chinese descent is brought to the emergency room by EMS, because of an episode of convulsive seizure.

Her parents report that at 2am they were awakened by a noise in the patient’s room. The patient was found shaking bilaterally, with asymmetric tonic posturing of the right arm.

EMS arrived at 2:15am, when the patient was postictal. A second seizure was observed at 2:20am and lorazepam was given IV at 2:25am.

The seizure resolved after this and the patient gradually returned to baseline while at the ER.

**Case 1 (cont’d):**

**PMH:**
- A similar nocturnal event occurred 2 weeks prior to this ER admission.
- Last menstrual period: 2 months ago
- Recent loss of weight (3kg in 2 weeks) with nausea, vomiting in the morning and mild frontal headaches. No history of fevers.

**FH:** Her mother and grandmother had epilepsy, both with nocturnal seizures.

**SF:** Sexually active, boyfriend was ex-IVDU, no precautions.

**Meds:** None taken so far.

**Allergies:** None known.

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**Case 1: Questions**

- Which antiseizure medication to start?
- What formulation?
- Can we predict toxicity / tolerability / allergic reaction?
- Any concerns for comorbid or associated conditions?
  - What if the patient is pregnant?
  - What if she is HIV+?
- Any additional considerations for the future medical management of this patient?

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**Case 2:**

- 6 month old boy is referred to the EMU for evaluation of daily clusters of head drops and occasional body flexion, starting 2 weeks prior to admission.
- On exam he has 3 white patches on his skin; can track past midline; cannot roll over yet, has some head lagging.
- Video-EEG reveals infantile spasms.
- MRI of brain is scheduled but not available at the time.

**PMH:** Birth history was unremarkable.

**FH:** First born son. The parents do not report FH of seizures or other neurological problems. The mother has facial angiofibromas.
Case 2: Questions:

• Which medication to start?
• Which formulation?
• Can we predict toxicity / tolerability / allergic reactions?
• Any concerns for comorbid conditions?
• Any considerations for the future management?

Case 3:

• 6 month old baby girl had her first febrile seizure at 5pm:
  — Temp 100.5°F.
  — Clonic seizure on the right, for 10min.
  — Postictal at the time of EMS arrival (5:20pm)
• 5:40pm: A second seizure on the way to the ER:
  - clonic seizure mostly on the left
  - 5:45pm: rectal diazepam was given by EMS, seizure resolves.
• 6pm: Arrival at the ER, postictal, gradually returns to baseline. Exam unremarkable.

**PMH:** Birth history was unremarkable. No prior history, normal development.

**FH:** First born child. No FH of seizures reported.

Outline of AET symposium

• Genomic approaches in selecting AETs: current therapy
  Norman Delanty, MD

• Personalizing drug delivery
  Emilio Perucca, MD

• Management of allergic reactions to AETs
  Bernard Cohen, MD

Outline of AET symposium

• Women issues in AET implementation
  Page B. Pennell, MD

• Management of seizures in HIV patients
  Gretchen L. Birbeck, MD MPH

• Conclusions
  Angus A. Wifong, MD

Learning Objectives from the AET symposium

• Develop a rational approach for the selection of the optimal antiepileptic formulation and delivery system for each individual patient with resulting increased adherence, efficacy, and tolerability.

• Recognize early adverse drug reactions and the patient populations at risk for developing them and implement treatment protocols that minimize such adverse outcomes.
**ARS Question 1**

Choose the **CORRECT** answer.

In the acute treatment of seizures:

A. Time to seizure cessation after dosing is faster with intranasal midazolam than with IV diazepam
B. Time to seizure control after decision to treat has been consistently found to be shorter for IV diazepam than buccal midazolam
C. IM midazolam stops seizures faster than IV lorazepam due to shorter time of drug preparation and delivery
D. In the prehospital treatment of status epilepticus, IV lorazepam is more effective than IM midazolam in terms of proportion of patients arriving to the ER free from seizures without rescue therapy

**ARS Question 2**

Choose the **WRONG** answer.

When treating an HIV+ person with epilepsy, it is important to consider:

A. Genotype resistance, prior to selection of an antiseizure drug
B. Monitoring Valproic acid (VPA) levels, virologic response, and Lopinavir/ritonavir (LPV/r) related toxicities
C. Avoiding antiseizure drugs that affect cardiac conduction (e.g., ß-blockers) with Saquinavir/r
D. Avoiding oral midazolam with most antiretrovirals

**ARS Question 3**

Which of the following AEDs does not reduce efficacy of oral contraceptive pills?

A. Phenytoin
B. Valproic acid
C. Carbamazepine
D. Topiramate
E. Oxcarbazepine

**ARS Question 4**

JS is a 32yo woman with TLE well-controlled on lamotrigine monotherapy and a combined oral contraceptive pill. She is planning to stop her birth control and try to conceive. What else can you do to further improve her chance of a healthy outcome for her and her unborn child?

A. Reinforce use of folic acid beginning prior to conception
B. Obtain a baseline LTG level now
C. Adjust LTG dose prior to conception to <300 mg per day if possible; lower dose after OCP is D/C
D. Obtain preconception LTG level on new dose without OCP
E. All of the above

**ARS Question 5**

Choose the **WRONG** answer:

A. Morbilliform rashes are never drug-induced
B. Risk factors for drug reactions include: female gender, increasing age, number of drugs, immunosuppression
C. Leukocytoclastic vasculitis can be caused by phenytoin
D. Acute generalized exanthematous pustulosis can be caused by carbamazepine
Genomic Approaches in Selecting AEDs
December 7, 2013
Norman Delanty, M.D.
Consultant Neurologist
Beaumont Hospital, and
Royal College of Surgeons in Ireland

Learning Objectives
• To understand how current advances in genomic medicine may impact on the care of patients with epilepsy
• To review how current research findings in epilepsy pharmacogenomics may facilitate optimum prescribing of antiepileptic drugs

Genomics
• The study of large sets of genes, or gene products, including the entire genome or the entire set of transcripts or proteins
• Sequencing technology now makes clinical genomics a reality
  • Disease-specific gene panels
  • Whole exome sequencing (WES)
  • Whole genome sequencing (WGS)
  • Next Generation Sequencing (NGS)

Pharmacogenomics
• Use of patient’s genomic information to help guide drug therapy, thereby optimizing and accelerating drug efficacy and minimizing or avoiding adverse effects of proposed therapy in that individual patient
• Use of genomic information to develop new drugs and identify new drug targets

Disclosure
Eisai
GSK Pharma
Lundbeck
UCB Pharma

Advisory Board Participation
Funding for Irish Epilepsy and Pregnancy Register

Personalized Medicine
• We try to practice “personalized” (patient-centered) medicine every day
• No two patients with epilepsy are the same
• Genomics should complement this approach to patient management
• We are on the cusp of a new genomic era in clinical medicine
Genomics 101

- 3.1 billion base pairs
- The exome comprises ~ 1.5 % of the genome
- Expanding understanding of the “introme”
- ~ 30,000 genes
- ~ 90,000 proteins
- Percentage of proteins where function understood unclear - ?? 23%
- Protein-protein interactions obviously important and complex

Types of Genetic Variation

- Polymorphism / mutation
- Inherited mutation
- De novo germ-line mutation
- Somatic mutation

Genetic Milestones in Epilepsy


Tools that are accelerating discovery in genetics:
- Linkage studies
- Candidate gene approach
- Genome-wide arrays (GWAS)
- Next-generation sequencing
- Common variation & CNVs
- Rare variation
- Exome & Genome sequencing

Role of Whole Exome Sequencing (WES)

- Research discovery in large disease areas
- Established, active…
- Diagnosis of known disorder
- New paradigm shift away from traditional genetic testing
- Discovery of new disorders in individual with unexplained disease
- Few centers offering this
- Truly translational
- Pharmacogenomic research – understanding individual drug response

Potential for Genomic Analysis in the Clinic

- Predict adverse drug reactions (ADRs)
- Predict response to AEDs
  - Broad response
  - Specific response
Pharmacogenomics and WES

- Best to look at extreme phenotypes
- Many examples in epilepsy
  - Hypersensitivity
  - Weight change
  - Teratogenicity
  - Vigabatrin retinopathy
  - Neuro-cognitive and psychiatric disturbance

AEDs and Adverse Drug Reactions

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<tr>
<th>AEDs</th>
<th>Adverse Drug Reactions</th>
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| Carbamazepine (CBZ) | Hypersensitivity 10%
  | Hyponatraemia 10-20% |
| Lamotrigine (LTG) | Hypersensitivity 10%
  | Insomnia 10% |
| Phenytoin (PHT) | Hypersensitivity 5%
  | Gum Hypertrophy 5% |
| Sodium Valproate (VPA) | Weight gain 30-40%
  | Tremor 20%
  | Thrombocytopenia 10%
  | Teratogenicity 10% |
| Vigabatrin (VGB) | Visual field constriction 40% |

Carbamazepine and Cutaneous Reactions

B*1502

Maculopapular Exanthema (MPE)
Mild rash; 1 in 20 first time users
Multiple organ involvement; 1 in 1,000
Stevens-Johnson Syndrome (SJS)
Life-threatening; 1-3 per 10,000 patients

Human Leukocyte Antigen-B*1502 is a complete predictor for CBZ-induced Stevens-Johnson Syndrome in Asia (Chung et al, Nature, 2004)

Could a similar genetic marker be found in non-Asians?

Applying GWAS to identify a genetic predictor for maculopapular exanthem (MPE)

43 CBZ-MPE cases
1339 Controls

Control frequency = ~3%, Case frequency = 14%
Odds ratio = 8.33 (3.6 – 19.4)

The same variant also predicts hypersensitivity syndrome (HSS)

22 CBZ-HSS cases
2619 Controls

Control frequency = ~2%, Case frequency = 20%
Odds ratio = 12.4 (1.27 – 121.03)

A Marker for all CBZ-cutaneous ADRs

OR (for any CBZ-ADR) = 25.93 (4.912 – 121.03)

For a patient testing positive:
5% → 26%

For a patient testing negative: 5% → 3.8%
A second predictive marker for cutaneous ADRs in epilepsy
- Small cohort sizes are perfectly capable of identifying high-risk variants
- Clear phenotypic definitions are essential
- Replication in independent cohorts

Levetiracetam Response
- “Dramatic” responders
- 10% response in previously refractory epilepsy
- Candidate gene association study in 247 English and 290 Irish patients failed to detect a significant association of common variation in SV2A, SV2B, and SV2C
- Rare variation in SV2A did not affect response to levetiracetam in 158 patients with focal and generalized epilepsy
  - Dihleus LM et al, Epilepsy Research, 2012
- Current GWAS / WES studies ongoing

SCN1A and AED Choice
- Dravet syndrome
- GEFS+
- Epileptic encephalopathy
- Other unrecognised patients
- Avoid sodium channels blockers
- Collective observed clinical wisdom
- Role of specific drugs
  - Stiripentol
  - Clobazam

Vigabatrin-related Visual Field Loss
- Irreversible visual field loss occurs in ~20-40% of patients on Vigabatrin
- Goldmann perimetry standard test
  - Relies on patient response
  - Difficult to quantify retinotoxicity
  - Impractical for detection of subtle changes over time
- Retinal nerve fibre layer thickness measured by Optical Coherence Tomography (OCT)

Sodium Valproate and Weight Gain
- Between 10-30% of patients experience severe weight gain over course of VPA treatment
  - Leading cause of treatment failure
  - Associated health disadvantages, risk for obesity and Type-II DM
  - Psychosocial implications among pediatrics

Current Collaborative Genomic Discovery Efforts in Epilepsy
- Epi4K.EPGP – NIH
- EpiPGX – FP7 (European Commission)
- EuroEpinomics
- EpimiRNA – FP7 (European Commission)
EpiPGX ADRs to date

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<tr>
<th>Reference ND: CBZ, LMT, PHT, OXC</th>
<th>177</th>
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<tbody>
<tr>
<td>Weight change</td>
<td>260</td>
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<tr>
<td>Neutropenia (CBZ, PHT)</td>
<td>57</td>
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<tr>
<td>Hyperammonia (CBZ, OXC)</td>
<td>54</td>
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<tr>
<td>Thrombocytopenia (CBZ, PHT)</td>
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<td>Thrombosis (CBZ)</td>
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<tr>
<td>Hyponatremia (CBZ, OXC)</td>
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<td>Thrombocytopenia (PHT, CBZ)</td>
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</tbody>
</table>

EpiPGX Call for Collaboration

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- Sanjay Sisodiya
s.sisodiya@ucl.ac.uk

Challenges for the new genomics

- Cost, and who pays?
- Incorporating genomics into mainstream medical practice
- Need for “genomic counselling”
- Challenge of incidental (actionable) findings
- Genomics in medical education
- “Minding and mining” the data through time
- Sharing the data with different health professionals
- Social and political acceptance and understanding

- Cavalleri GL and Delanty N, 2012.

Integrating Phenotype and Genotype in the Clinic

Impact on Clinical Care and Practice

- Limited current impact
  - CRZ rash
  - SCN1A and drug choice
- Delay in translating to clinic:
  - More positive findings will accelerate
  - Cost benefit
- Current collaborative ongoing

“….this moment constitutes a watershed in the history of genetics in medicine.”

Hunter DJ, Altshuler D, and Rader DJ.
“Mining the Genome for New Biology”
NEJM, June 28th, 2008.
The Future

- Clinical medicine will continue as always
- The importance of bedside communication
- Formulation of a differential diagnosis and management plan
- The importance of common sense
- Routine exome sequencing from birth to function as a "individual health repository" for that patient throughout life
- Early use of WES when "micro-etiology" unclear
- Use of pharmacogenomic markers to guide therapy
- More collaborative
- More data-centric

Some Websites

- www.hgmd.org
- www.pantherdb.org
- www.epigen.org
- www.epgp.org/epi4k
- www.epipgx.eu
- www.pharmgkb.org
- www.uniprot.org

Acknowledgements

- Epilepsy Programme, Beaumont Hospital
- Gianpiero Cavalleri, RCSI
- Mark McCormack, RCSI
- David Goldstein, CHGV, Duke University
- Lisa Slattery, RN, RCSI
- Cathal Kelly, CEO, RCSI
- EPIGEN colleagues
- Epi4K
- EpiPGX
Personalizing Drug Delivery
December 7, 2013

Emilio Perucca, M.D., Ph.D.
Clinical Pharmacology unit, University of Pavia
&C. Mondino National Neurological Institute,
Pavia, Italy

American Epilepsy Society | Annual Meeting

Disclosure
Name of Commercial Interest
Type of Financial Relationship
Eisai, GSK, Viropharm
Speakers’ fee
GSK, Lundbeck & Viropharma
Advisory board

Learning Objectives
• Develop rational criteria to personalize choice of delivery systems, routes of administration and dosing regimens
• Acquire familiarity with advantages, limitations and indications of unusual ways of delivering anti-seizure medications

Personalizing Treatment is More than Deciding What to Give: Tusko’s Story

♣ On August 3, 1962, the “prize of Oklahoma City Zoo” was injected with LSD using a mg·kg⁻¹ dose previously used in cats
♣ “Within 5 min, Tusko trumpeted, collapsed, fell heavily onto his right side... and went into status epilepticus...”
♣ Despite several unsuccessful attempts to control the seizures, about one hour later Tusko was dead.

West et al. Science 1962;138:1100–1103

Personalizing Treatment is More Than Deciding How Much To Give

♣ Which is the best formulation or delivery system for the individual patient or situation?
♣ How should the dose be divided?
♣ Which is the most appropriate route of delivery?

Personalizing Formulation: ‘flatter is better’?

Serum AED Concentration Profiles at Steady-State vs Risk of Toxicity or Seizure Breakthrough – Narrow Therapeutic Index Drug

Immediate-release formulation (b.i.d.)
Controlled-release formulation (o.i.d.)
Threshold concentration for toxicity
Minimum concentration required for seizure control
FDA-Approved Extended-Release Formulations of AEDs

<table>
<thead>
<tr>
<th>Active Principle</th>
<th>Brand name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Carbatrol</td>
<td>Shire</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol CR, Tegretol XR</td>
<td>Novartis</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Depakote ER, Depakote DR</td>
<td>Abbott</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal XR</td>
<td>GSK</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Keppra XR</td>
<td>UCB</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Apydan Extent</td>
<td>Supernus</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Ostelian XR</td>
<td>Various</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin, Dilantin-125, Prompt, Phenytek, Dilantin Capsules, Di-Phen</td>
<td>Various</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Trokendi XR</td>
<td>Supernus</td>
</tr>
</tbody>
</table>

*FDA-Approved* Extended-Release Formulations of AEDs

*Tentative approval June 2013*

Leppik & Hovinga. Epilepsia 2013;54:28-35 (updated)

---

**What Difference Can a Formulation Make?**

Comparison of Two Double-Blind Trials of Carbamazepine in the Elderly

<table>
<thead>
<tr>
<th>Brodie et al., 1999</th>
<th>Saetre et al., 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>71%</td>
<td>73%</td>
</tr>
<tr>
<td>N = 102</td>
<td>N = 93</td>
</tr>
<tr>
<td>42%</td>
<td>67%</td>
</tr>
<tr>
<td>N = 48</td>
<td>N = 91</td>
</tr>
</tbody>
</table>


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**Extended-Release Formulations: Potential Advantages and Concerns**

- **Advantages**
  - Lesser fluctuation in serum drug levels
  - Most valuable for patients susceptible to peak concentration-related side effects
  - Benefits in convenience, and possibly in compliance

- **Concerns**
  - Lack of comparative data with the IR formulation - are there advantages, and if so for whom?
  - Any risks with switching?
  - Shorter forgiveness period?
  - Cost-effectiveness?

IR = immediate-release

---

**Double-Blind Randomized Trial of Controlled Release (CR) vs Immediate-Release (IR) Carbamazepine**

Cross-over trial in 48 patients with seizures or intermittent side effects

Physicians asked to optimize dose while trying to minimize dosing frequency

Dose optimization followed by 1-month evaluation

Percentage Distribution of Seizures Over 24-hour Periods in 41 Consecutive Children with Frontal Lobe Seizures

Distribution of Frontal and Temporal Lobe Seizures vs Time of the Day from a Study of 44 Adults and Children

Higher Evening AED Dose for Nocturnal and Early Morning Seizures

- Retrospective analysis of 17 children with uncontrolled nocturnal or early morning seizures
- All children were switched to a proportionally higher evening AED dose without changing the total daily dose
- After a mean follow-up of 5.3 months, 11 became seizure-free and 4 had 75-90% reduction in their seizures

Personalising Route of AED Delivery Special Situations

- Inability to take solid dosage forms (e.g., infants, young children)
- Malabsorption syndromes
- Inability to take oral medications
- Need for emergency treatment

Superiority of i.m. Midazolam (MDZ) over i.v. Lorazepam (LRZ) for Prehospital Treatment of Status Epilepticus

Diazepam: Speed of Rectal Absorption in Infants

*Primary endpoint (% arriving to ER free from seizures without rescue therapy)

Intramuscular midazolam is not FDA-approved for prehospital treatment of status epilepticus


A Shortcut from the Nose to the Brain: Intranasal Delivery

- Bypasses blood—brain barrier and first-pass effect
- Easily applicable in convulsing and first-pass effect
- Only feasible for potent AEDs (>20 mg/dose)
- Absorption generally better for lipophilic drugs
- Solubilization issues with some agents
- Concerns with inter-subject variability, impact of nasal pathology and local irritation
- Evidence of anti-seizure effectiveness best provided for midazolam and lorazepam

Randomized Trial of Sublingual Lorazepam vs Rectal Diazepam in 436 Children with Convulsions

- Seizure cessation in 5 min (%)
- Seizure cessation in 10 min (%)
- Seizure cessation in 20 min (%)

Dose was 0.5 mg/kg for rectal diazepam and 0.1 mg/kg for sublingual lorazepam

Buccal midazolam and sublingual lorazepam are not FDA-approved for treatment of convulsions

Mala CK et al., J Child Neurol 2013; July 31 pub ahead of print

Is the Rectal Route Feasible for Short-Term Substitution in AED Therapy?

- Feasibility demonstrated
  - Carbamazepine
  - Lamotrigine
  - Levetiracetam
  - Phenobarbital
  - Topiramate
  - Valproic acid

- Feasibility questioned
  - Felbamate
  - Gabapentin
  - Oxcarbazepine
  - Phenytoin

Randomized Trial of Buccal Midazolam vs Intravenous Diazepam in 122 Children with Convulsions

- Seizure cessation (%)
- Time to effect after dosing (min)
- Time to effect after decision to treat (min)

Dose was 0.3 mg/kg i.v diazepam and 0.3 mg/kg for buccal midazolam

Buccal midazolam is not FDA-approved for treatment of convulsions

Anderson and Saneto, Adv Drug Deliv Rev 2012;64:911-8

Randomized Trial of Buccal Midazolam vs Rectal Diazepam in 122 Children with Convulsions

- Success rates in 3 Double-Blind Trials of Buccal Midazolam (MDZ) vs Rectal Diazepam (DZP) in Children with Convulsions

Success rates in 3 Double-Blind Trials of Buccal Midazolam (MDZ) vs Rectal Diazepam (DZP) in Children with Convulsions


- *Cessation of seizures within 10 min (without recurrence in 1 h for studies 1 and 3)

Buccal midazolam is not FDA-approved for treatment of convulsions


A Shortcut from the Nose to the Brain: Intranasal Delivery

- Bypasses blood—brain barrier and first-pass effect
- Easily applicable in convulsing or non-collaborative patients
- Only feasible for potent AEDs (>20 mg/dose)
- Absorption generally better for lipophilic drugs
- Solubilization issues with some agents
- Concerns with inter-subject variability, impact of nasal pathology and local irritation
- Evidence of anti-seizure effectiveness best provided for midazolam and lorazepam

Misra and Kher, Curr Pharm Biotech 2012;13:2355-79

Rapid Onset of Action of Rectal Diazepam in Preventing Seizure Recurrence in Children with Acute Repetitive Seizures (n=133)

Probability of No Seizure for Rectal Diazepam vs Placebo

- MDZ
- Diazepam


11/19/2013
Randomized Trial of Intranasal Midazolam vs Intravenous Diazepam for Acute Childhood Seizures (n=50)

- Seizure cessation (%)
  - DZP: 80%
  - MDZ: 67%
- Time to effect after dosing (min)
  - DZP: 3.01
  - MDZ: 6.67
- Time to effect after arrival to ER (min)
  - DZP: 25
  - MDZ: 16

All children had been convulsing for >10 at time of enrolment. Dose was 0.3 mg/kg for i.v. diazepam and 0.2 mg/kg for intranasal midazolam.

Factors to be Considered in Personalizing Emergency Treatment in a Convulsing Child

- Setting (hospital vs pre-hospital – household vs ambulance)
- Ease of access to an i.v. line
- Availability and regulatory status of specific medications / formulations
- Appropriateness of providing rescue medication (history of prolonged seizures and seizure clusters, skills and collaboration of family members, distance from nearest hospital, etc.)
- Perceived risk/benefit ratio of different treatment options (or no treatment) in the child
- Cost and affordability

Innovative Delivery Systems for Personalized AED Therapy in the Future

- Novel formulations (microspheres, microemulsions, liposomes, proliposomes, nanoparticles, exosomes, ethosomes, dendrimers) including multifunctionalized nanoparticles targeting specific brain sites
- Intracerebroventricular, convection-enhanced and polymeric brain delivery systems
- Imaging-guided brain drug delivery
- Conditional response devices, e.g. drug delivery systems triggered by epileptic activity or changes in brain state preceeding seizure onset

Targeted Drug Delivery at the Site of the Epileptic Focus: The Subdural Hybrid Neuroprosthesis

The subdural hybrid neuroprosthesis is not FDA-approved for treatment of seizures.

Conclusions

- Efficacy and tolerability of an AED depend on modality of delivery – formulation, dosing scheme and route
- Delivery needs to personalised based on the clinical situation and the individual’s characteristics
- Innovative ways of delivering AEDs could lead to major therapeutic breakthroughs in the future
Personalized Medical Care: Recognition, Management, and Maybe Prevention of Cutaneous Hypersensitivity Reactions

Bernard A. Cohen, M.D.
Johns Hopkins Children’s Center
Baltimore, Maryland

Learning Objectives

• Survival dermatology: Primer on systematic approach
  - Clues: gestalt, distribution, pattern recognition, anatomic depth, distribution, setting, other clues
• Pattern recognition: viral exanthem models
• Pattern recognition: specific drug reactions
• Management
• Risk factors and prevention

Drug Reactions: Epidemiology

• Cutaneous reactions cause 3% of disabling “injuries” during hospitalization
• 0.1-0.3% associated with mortality
• Risk factors: female, increasing age, number of drugs, immunosuppression
• Eg. HIV 10-15X risk with sulfonamides
• Resources: Boston Collaborative Drug Surveillance Program

Drug Reactions: Pathogenesis

• Hypersensitivity reactions/immunologic?
  - IgE dependent (type I)
  - Cytotoxic (type II)
  - Immune complex (type III)
  - Cell mediated (type IV)
• Non-immunologic
  - Overdose, pharmacologic side effects, cumulative/delayed toxicity, drug-drug interaction, alteration in metabolism, exacerbation of disease
• Idiosyncratic (possible immunologic)
  - DRESS, TEN/SJS, in HIV setting, Drug-induced lupus
• Importance of Immunologic parameters and genetic predisposition (stay tuned)

Disclosure

Nothing to disclose
Systematic Evaluation: History

- How long, chronology?
- Does it itch, hurt?
- Self treatment?
- Other drugs?
- Myths?
Systematic Evaluation: Exam

- Good light
- Good skin exposure
- Good eye
- Good book

Systematic Evaluation: General Considerations

- General health, chronology
- Distribution
- PATTERN
- Organization
- Morphology
- Anatomic depth
- Tumor v inflammatory

Sun Exposed Sites

- Phototoxic reactions (sun burn)
- Photoallergic reactions (eg. drug)
- Psoriasis (isomorphic phenomenon)
- Polymorphous light eruption
- Porphyria
- Lupus erythematosus
...and the age of the patient

- Variable morphology of the rash
- Variable course
- Variable exposure/susceptibility
- Variable incidence of disease

Immunologic Parameters

- Hereditary immunodeficiency
- Acquired immunodeficiency
- Drug-induced immunosuppression
- Cutaneous diseases in transplantation
Inside v Outside Job

- How did the eruption get there?
- Localized?
  - Contact reaction
  - Primary cutaneous inoculation
  - Local reactivation
- Disseminated?
  - Reactive process (viral, drug, immunologically mediated)
  - Embolic
  - Toxin mediated

Although
morbilliform=exanthematous=
maculopapular


Measles

- Measles virus, genus Morbillivirus, family Paramyxoviridae
- Respiratory droplet spread
- 7-10 day incubation → 2-4 day prodrome (cough, coryza, conjunctivitis, Koplik spots)
- 10 day skin eruption
- DEFINES MOST COMMON DRUG REACTION PATTERN

Measles=morbilliform

Amoxicillin induced morbilliform eruption

Enteroviral exanthem...
morbilliform eruption

Measles

- Measles virus, genus Morbillivirus, family Paramyxoviridae
- Respiratory droplet spread
- 7-10 day incubation → 2-4 day prodrome (cough, coryza, conjunctivitis, Koplik spots)
- 10 day skin eruption
- DEFINES MOST COMMON DRUG REACTION PATTERN
Morbiliform (Exanthematous) Drug Reactions

- Most common cause cutaneous reactions
- Type IV, drug or metabolite binds MHC II-peptide complexes, cytotoxicity results in keratinocyte necrosis
- May be potentiated by viral infections (HHV6, HIV, adenovirus, EBV, CMV, Parvovirus B19)
- 7-14 days after initiation of med
- 1% of most drugs, but increased with aminopenicillins, sulfonamides, cephalosporins, ANTICONVULSANTS
- Usually resolve, occasionally marker for more severe reaction

Urticaria...

urticaria

Urticaria, Angioedema, Anaphylaxis

- IgE mediated type I reaction
- Edematous papules, expanding plaques, angioedema with deeper lesions
- Transient <24 hours, migratory
- Urticarial vasculitis >24 hours
- Acute < 6 wks v chronic
- Drugs: aminopenicillins, cephalosporins, sulfonamides, erythromycin, tetracycline
- Skin testing for PCN only

Graft v host disease…sort of morbilliform too

Scarlet fever
Scarlet Fever-2nd Disease

- Pyrogenic exotoxin producing group A beta-hemolytic streptococcal infection
- Early 20th century-toxin A
- 1950’s-toxin types C and B
- Risk of Rheumatic fever/serious complications declined before introduction of antibiotics
- DEFINES <5% OF DRUG REACTION PATTERNS

What else can give you a scarlatiniform eruption and a strawberry tongue?

- Staphylococcal infection
  (Staph/strep TSS)
- Viral exanthem
- Drug reaction
- Kawasaki syndrome

Vasculitis-Clinical pattern that you must know!

- Palpable purpura-destruction of small vessels
- Infectious (and non-infectious)
- Infections=fever, sick patient (usually)
- May be life-threatening
- Early recognition and treatment life-saving
- DEFINES <5% OF DRUG REACTION PATTERNS, BUT IMPORTANT TO MAKE DX, RECOGNIZE SYSTEMIC SX’S

Leukocytoclastic Vasculitis
Leukocytoclastic Vasculitis

- 7-21 days after initiation of med
- 3-5 days on rechallenge
- Penecillins, NSAID’s, sulfonamides, cephalosporins, PTU, thiazide diuretics, allopurinol, PHENYTOIN, biologic agents, hydralazine, minocycline
- Often restricted to skin but may be systemic

Fixed Drug Eruption

- Recurrent itchy violaceous plaques/target lesions with admin of same drug
- NSAID’s, sulfonamides, BARBITURATES, tetracyclines, CARBAMAZEPINE
- Red acutely, PIH following D/C of drug
- Lips, trunk, legs, arms, genitals
- Systemic reactions unusual
- More common in adults
- Cause unclear but “memory” T-cell resides in dermis
- Tx: stop the drug

Staphylococcal scalded skin syndrome...exfoliative toxin...superficial epidermal cleavage, mucous membranes spared

v. Stevens-Johnson syndrome (or TEN)... drug-induced injury with skin cleavage at basement membrane zone, severe mucous membrane involvement

SJS/TEN

- Spectrum of ds or distinctive
- SJS: at least 2 mucous membranes <40-30% BSA
- SJS 1.2-6/million people/yr
- TEN 0.4-1.9/million people/yr
- HIV 1/thousand people/yr (antiretroviral use)
- 80-95% assoc with drugs
- 1-8 weeks after initiation of drug, within hours on reexposure
- Morbilliform, atypical targetoid lesions
- Widespread flaccid bullae, erosions, ulceration of skin, inflammation and ulceration of mouth/mmm
**SJS/TEN Systemic Disease**

- Conjunctivae, trachea, bronchi, gut, kidney
- Acute renal failure, ATN
- 25% pulmonary dysfunction, adult RDS, fibrosis
- Anemia, leukopenia, hepatitis
- Abdominal pain, diarrhea
- Encephalopathy, myocarditis

**SJS/TEN: Pathogenesis**

- T-cell mediated process
- CD8+ trigger keratinocyte necrosis
- Drug noncovalently bind to MHC and TCR vs metabolites of drugs binding covalently to cellular peptides that stimulate immune sys
- Apoptosis causes cell death with upregulation of CD8+ cells and granzyme B/perforin, soluble Fas ligant, NO, TNFalpha

**Highest Risk Drugs**

- Nevirapine
- Lamotrigine
- Carbamazepine
- Phenytoin
- Antibiotic sulfonamides
- Allopurinol
- Oxicam NSAID’s
- Also Aminopenecillins, cephalosporines

**SJS/TEN: Prevention!**

- Relationship to MHC allotype
- For aromatic seizure meds (carbamazepine, phenytoin, oxcarbazapine, lamotrigine and HLA-B*1502 and allopurinol and HLA-B*5801 in Han Chinese
- HLA-B*1502 and carbamazapine in Thai, Malaysian, South Indians
- HLA-B*5801 and allopurinol in W Europeans
- HLA-B*5701 and abacavir
- HLA-A*3101 and carbamazepine in Europeans

**SJS/TEN: Management**

- Systemic steroids, IVIG, cyclosporine, etc not proven better than supportive measures
- No repeat exposures
- Genetic HLA testing for East Asians before starting aromatic meds or abacavir
- Immediate cessation of med
- Burn unit management

**19-year-old girl with 2 week history of high fever, increasing white count, eosinophilia, hepatitis...**

- Drug reaction with eosinophilia and systemic symptoms
- DRESS
- Old phenytoin reaction/anticonsultant hypersensitivity reaction
- Dramatic elevation of HHV6
**DRESS**

- Drug eruption: generalized edema, morbilliform rash, tense bullae, lip erosions
- No epidermal sloughing
- Fever, multiorgan involvement
- Pharyngitis, cervical adenopathy
- Atypical lymphocytosis, eosinophilia
- Hepatitis, interstitial nephritis, pneumonitis, encephalitis and (thyroiditis, carditis, pancreatitis, epididymitis, myositis, etc)

**DRESS: Epidemiology**

- On first exposure to med
- 1-6 weeks post exposure
- 1:3,000 exposures
- Aromatic anticonvulsants, lamotrigine, sulfonamide antibiotics, dapsone, minocycline allopurinol, vevaripine

**DRESS: Management**

- Family history (possibly AD inheritance)
- Stop drug asap, supportive care
- Role of systemic steroids?
- Symptoms may persist or recur for months
- Complications (renal, hepatic, pulmonary)

**Acute Generalized Exanthematous Pustulosis (AGEP)**

- Acute onset of nonfollicular pustules on edematous red base, fever, facial edema, target lesions, purpura, vasculitis, blisters,
- Mucosal erosions in 50%
- Short period of sensitization, topical or systemic
- Clinical findings and course overlap with DRESS, TEN

**AGEP and Anticonvulsants**

- May overlap with TEN.

**Take home!**

- Know your drug eruptions especially markers for severe reactions
- Know you skin exam: full skin exam including mucous membranes, palms and soles, genitals
- Know your patients: risk factors, HLA markers, personal or family history of reactions
- When in doubt stop the drug, sooner the better
- Know when to call your friendly neighborhood dermatologist
Bibliography: General


Bibliography

- SJS/TEN

- DRESS

- AGEP
Women’s Issues in AET Implementation
December 7, 2013
Page B. Pennell, MD
Director of Research, Division of Epilepsy
Division of Women’s Health
Brigham and Women’s Hospital
Harvard Medical School

Learning Objectives

• Select optimal therapies for women with epilepsy during reproductive years to minimize adverse consequences to their reproductive health

• Gain understanding of how to best select type of AED AND amount of AED during different stages of pregnancy to improve maternal and child outcomes

Disclosure

Name of Commercial Interest | Type of Financial Relationship
--- | ---
None | None

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Dr. Pennell serves as a volunteer member of the Board of Directors of the American Epilepsy Society and of the Professional Advisory Board of the Epilepsy Foundation.


Progesterone Treatment Trial

- Randomized, double-blind, placebo-controlled, Phase III, multicenter clinical trial (n=294)
  - Stratified by catamenial and non-catamenial status
- Treatment: progesterone or placebo (2:1)
  - Progesterone oral lozenges
    - 200 mg TID 14-25, 100 mg TID 26-27, 50 mg TID 28, then stop
  - 3 baseline months and 3 treatment menstrual-cycles
- No difference in Responder Rates (both groups)
- Secondary analysis
  - C1 exacerbation level was a predictor of response to Progesterone


Responder rates with progesterone and placebo treatment vs perimenstrual (C1) catamenial level of seizure exacerbation


Perry Natal Case Hx

- March 2012 – 40 yo G5P3, presents at 6 4/7 weeks GA
- Epilepsy onset – 18yo, college freshman
  - 1) Auras described as feeling “flu-like” & slowed down, then numbness all over. Can progress to LOA, and post-ictal grogginess. Most recent 2006.
  - 2) Evolve to GTCS. Most recent 2000 during VPA wean.
- Brain MRI – periventricular heterotopias

- Pregnancy Hx:
  - 1st FT pregnancy: on VPA, autism, MR, PVH
  - 2nd FT pregnancy: on LTG, Postpartum ataxia unable to walk
  - 3rd FT pregnancy: on LTG, twin demise, some speech delay
- Recent LTG levels: 6 – 12 ucg/mL
- Current meds: LTG 200 BID, folic acid 4 mg QD
- TDM plan started: Break-through seizure at 20 weeks EGA

Magnitude

- 1.3 million women of child-bearing age in US with epilepsy
  - Most common neurologic disorder requiring daily treatment, and one of the most common disorders requiring known teratogens
  - 25,000 AED-exposed babies per year born in US to WWE (0.6%)
- More pregnancies on AEDs due to other indications, 3.5%
- Teratogenic effects on offspring significant
  - Increased frequency of MCM in offspring of women on AEDs
    - Cardiac defects, oral clefts, urologic defects, neural tube defects, skeletal
  - Neurodevelopmental defects common, with lifelong consequences
  - Clinical dilemma of minimizing teratogenic effects of AED exposure while maintaining maternal seizure control
  - Prognosis improved with planned pregnancies

**Strong Inducers**
- phenobarbital
- phenytoin
- carbamazepine
- primidone
- oxcarbazepine

**Weak Inducers**
- topiramate
- levetiracetam
- valproate
- rufinamide
- clobazam
- tiagabine

**Non-inducers**
- ethosuximide
- lamotrigine
- oxcarbazepine
- carbamazepine
- valproate
- lamotrigine

---

**Carbamazepine & COCs PK & PD Study**

- **Specific Aim:** to determine if changes in ethinyl estradiol (EE) and the progestin levonorgestrel (LNG) permitted ovulation.

- **Methods:** DB, randomized cross-over study
  - CBZ 600 mgs or placebo x 2 months, with low-dose COC (EE 20 ug, LNG 150ug)
  - Ovulation detected by twice weekly sonography and PROG assays.

- **Results:** 10 completers (5 discontinued due to CBZ SEs)
  - Mean area under the curve (AUC) lower during CBZ use compared to placebo
    - EE (1,778 vs. 986 pg*h/ml, p < 0.001)
    - LNG (24.8 vs. 13.8 pg*h/ml, p = 0.04)
  - Ovulation occurred in 5/10 CBZ cycles compared to 1/10 placebo cycles (ns)
  - Breakthrough bleeding occurred in 8 /10 CBZ cycles and 2/10 placebo cycles (ns)

- **Conclusion:** Women treated with CBZ are not adequately protected from pregnancy by low-dose OCs.

---

**Contraceptive Choices for Women**

<table>
<thead>
<tr>
<th>Method</th>
<th>Efficacy</th>
<th>Reversibility</th>
<th>Duration of Use</th>
<th>Ovulation inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive pill</td>
<td>88.54%</td>
<td>Immediate</td>
<td>Daily</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>88.96%</td>
<td>Immediate</td>
<td>Monthly</td>
<td>Yes</td>
</tr>
<tr>
<td>Subdermal implant</td>
<td>88.94%</td>
<td>Delayed*</td>
<td>3 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>99%</td>
<td>Immediate</td>
<td>5 years</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Levonorgestrel IUD</td>
<td>99%</td>
<td>Immediate</td>
<td>25 years</td>
<td>No</td>
</tr>
</tbody>
</table>

*Approved Quality Measure for Epilepsy

---

**Long-Acting Reversible Contraceptives (LARC)**

- Copper TUD
- Mirena IUD (levonorgestrel)
- Contraceptive implant (etonogestrel)

---

**Lamotrigine Hormonal Contraceptives, PK & PD**

- **LTG serum concentration-to-dose ratio was significantly lower in EE than control group.**
- 0.030 (± 0.004) vs. 0.017 (± 0.006)

- **No difference in women using progesterins only compared to controls.**

- Baseline LTG levels reached at an average of 8.0 (SD 3.69) days after the start of COCs.
- 27 women had seizure worsening, correlating with the lower concentrations.
Other AEDs with lower concentrations on ethinyl estradiol

- Valproic acid
  - VPA plus COC group: VPA conc were lower than VPA alone group, with a median decrease of 23.4%
- Oxcarbazepine likely
  - Theoretical, based on glucuronidation pathway and reports of increased clearance during pregnancy
- The CDC Medical Eligibility Criteria labels LTG monotherapy as Category 3 (risks generally outweigh the benefits) for use with COC


Risk of AEDs during Pregnancy

Risk of in utero AED exposure

- Major Congenital Malformations (MCM)
  - 1.5 – 3% in general population; OR 2-4 in WWE on AEDs
- Neurodevelopmental delay
- SGA, microcephaly, minor anomalies

AED Pregnancy Registries

- EURAP: An international registry of AEDs and pregnancy
- North American AED Pregnancy Registry
- UK Epilepsy and Pregnancy Registry
- Australian Pregnancy Register
- Kerala Pregnancy Registry, India
- Pharmaceutical company registries

Risk of major malformations by average valproate dose (mg) during the first trimester


**NEAD STUDY DESIGN**

- Multicenter prospective, parallel-group observational study with statistical control.
- 309 pregnant mothers with epilepsy enrolled from late 1999 to early 2004 in USA & UK.
- Antiepileptic drug (AED) monotherapy: 
  - Carbamazepine (CBZ)
  - Lamotrigine (LTG)
  - Phenytoin (PHT)
  - Valproate (VPA)
- Blinded cognitive assessments: 2, 3, 4.5, & 6 y/o
- Primary outcome: IQ at 6 y/o

---

**Fetal Exposure to Valproate Associated with Lower IQ at Age 6**

Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age & folate:

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>LTG</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ</td>
<td>105*</td>
<td>108*</td>
<td>108*</td>
<td>97</td>
</tr>
<tr>
<td>Difference</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>DCIs</td>
<td>(3:12)</td>
<td>(6:15)</td>
<td>(5:16)</td>
<td></td>
</tr>
<tr>
<td># Children</td>
<td>93</td>
<td>100</td>
<td>56</td>
<td>62</td>
</tr>
</tbody>
</table>

* Significantly better than VPA.

CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate


---

**Dose-Dependent Effects in NEAD**

- Carbamazepine
- Lamotrigine
- Phenytoin
- Valproate


---

**Risks of Seizures versus Antiepileptic Drugs**

- **Generalized Tonic-Clonic Seizures**
  - Fetal bradycardia (>20-30 min)
  - Maculopathy & stillbirths
  - Developmental delay (>5 GTCS during pregnancy)

- **Status epilepticus**
  - 30% maternal mortality; 50% infant mortality

- **Maternal Risks**
  - Death rate during pregnancy in women with epilepsy increased X10, primarily due to seizures in UK study
  - Trauma, diphtheria, SUDEP, drowning

- **Neonatal outcomes**
  - Seizures all types associated with SGA & premature delivery

**Seizure Frequency during Pregnancy (compared to first trimester)**

![Seizure Frequency Chart](image)


**Physiological Changes in Pregnancy: Effects on Drug Disposition**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Total body water; etc fluid</td>
<td>Altered drug distribution</td>
</tr>
<tr>
<td>↑ Fat stores</td>
<td>↓ Elimination of lipid soluble drugs</td>
</tr>
<tr>
<td>↑ Cardiac output</td>
<td>↑ Hepatic blood flow, ↑ elimination</td>
</tr>
<tr>
<td>↑ Increased RBF; ↑ GFR</td>
<td>↑ Renal clearance of unchanged drug</td>
</tr>
<tr>
<td>Altered CYP/UGT activity</td>
<td>Altered systemic absorption &amp;/or hepatic elimination of 50% of drugs</td>
</tr>
<tr>
<td>↓ Maternal albumin</td>
<td>Altered free fraction; increased hepatic extraction</td>
</tr>
</tbody>
</table>

Battino D, EURAP. *Neurology*. 2006; Battino D, EURAP. *Epilepsia* 2013.

**Clearance**

Daily dose (mg/kg)

AED concentration (mg/L)

**Total and Free LTG Clearance Across Pregnancy (n=53 Pregnancies, 305 Samples)**

![Clearance Graph](image)


**Proportion of Patients That Had Worsening of Seizures Above Their Baseline With the Use of TDM**

- Ratio to target concentration of 0.65 predicts increased seizure risk
- Empiric taper of LTG over 10 days reduced postpartum toxicity (p<0.05)

![Proportion Graph](image)


**Lamotrigine Clearance during Pregnancy**

![Lamotrigine Graph](image)

Major routes of elimination of AEDs

<table>
<thead>
<tr>
<th>Route of Elimination</th>
<th>AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal excretion*</td>
<td>Levetiracetam, Pregabalin, Vigabatrin, Topiramate</td>
</tr>
<tr>
<td>Cytochrome P450 metabolism†</td>
<td>Phenytoin, Phenobarbital, Carbamazepine, Zonisamide</td>
</tr>
<tr>
<td>Glucuronidation*</td>
<td>Valproate, Lamotrigine, Oxcarbazepine</td>
</tr>
</tbody>
</table>

* Main route of metabolism
† Highly protein bound

Pharmacokinetic Changes in AEDs During Pregnancy

<table>
<thead>
<tr>
<th>AED</th>
<th>Decreases in Total Concentrations</th>
<th>Increase in Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEV</td>
<td>60%</td>
<td>243%</td>
</tr>
<tr>
<td>LTG</td>
<td>36–62%</td>
<td>65-230%</td>
</tr>
<tr>
<td>OXC</td>
<td>55% (free 50%)</td>
<td>60%</td>
</tr>
<tr>
<td>PB</td>
<td>60-70%</td>
<td>19-117%</td>
</tr>
</tbody>
</table>

- Evidence for a change in clearance or levels of VPA, FRM, ESX, CBZ is conflicting or lacking.


Clinical impact of Gestational-induced Changes in Clearance

- Evidence of a change in clearance or levels of VPA, FRM, ESX, CBZ is conflicting or lacking.

Risk for seizures deterioration higher in a) patients w. seizures in previous 12 months and in b) focal epilepsy. When ABL < 65% from preconception baseline, seizures worsened significantly during the 2nd trimester.

Carbamazepine Clearance and Seizure Control in Pregnancy

- CBZ is commonly used during pregnancy in WWE worldwide.
- Data on CBZ clearance is conflicting. Current AAN guidelines state monitoring of CBZ levels should be considered. However, the clinical utility of TDM is unclear.

**Background:** CBZ is commonly used during pregnancy in WWE worldwide. Data on CBZ clearance is conflicting. Current AAN guidelines state monitoring of CBZ levels should be considered. However, the clinical utility of TDM is unclear.

**Methods:**
- Prospective observational study (n= 152 samples in 16 pregnancies in 13 WWE)
- Total & free CBZ, total & free CBZ-epoxide (CBZ-EPO) concentrations measured
- Free fraction (free / total concentration) of CBZ & CBZ-EPO calculated
- Apparent oral clearances (mg/kg)/(mg/mL) calculated for each compound

- Analyses:
  - Change in clearance of each compound & free fractions in each trimester
  - Seizure frequency (SzF) examined for association with changes in total & free CBZ and CBZ-EPO concentrations, using a ratio to target concentration of <0.65 as predictive of increased seizures.

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  - Seizure frequency (SzF) examined for association with changes in total & free CBZ and CBZ-EPO concentrations, using a ratio to target concentration of <0.65 as predictive of increased seizures.
Results:

- Figure 1. Increase in Free Fraction of CBZ and CBZ-EPO through pregnancy (p<0.01)
- No significant change in clearance of total or free CBZ or CBZ-EPO
- RTC <0.65 not correlated with increased SzF for total or free CBZ or CBZ-EPO concentrations

Discussion:

- The increase in free fraction of CBZ & CBZ-EPO during pregnancy may help protect against seizure worsening.
- There was no clear relationship between decreased concentrations & increased SzF.
- TDM of CBZ during pregnancy may not be necessary when resources are limited.
- A larger prospective multi-center study is necessary to confirm these findings.

Supported by NIMH P50 MH 6803 and NINDS 2U01NS038455.

Presented at 2013 AAN Annual Meeting.

Pathways/Interactions of Medication Exposure in Pregnancy

Objectives

1. Therapeutic Monitoring Guidelines for Pregnancy
2. Determine Fetal Medication Exposure
3. Identify Factors Influencing #1,2
4. Effects of type of AED and Level of Exposure on Fetal Outcomes

AEDs in Breast Milk

<table>
<thead>
<tr>
<th>AED</th>
<th>Breastmilk Concentration</th>
<th>Adult t1/2</th>
<th>Neonate t1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>0.06-0.41</td>
<td>9-25</td>
<td>0-36</td>
</tr>
<tr>
<td>PHT</td>
<td>0.06-1.19</td>
<td>15-15</td>
<td>15-155</td>
</tr>
<tr>
<td>PR*</td>
<td>0.06-0.46</td>
<td>75-125</td>
<td>150-300</td>
</tr>
<tr>
<td>ESZ</td>
<td>0.06-1.55</td>
<td>32-60</td>
<td>32-38</td>
</tr>
<tr>
<td>PNP</td>
<td>0.72</td>
<td>4-12</td>
<td>7-60</td>
</tr>
<tr>
<td>VPR</td>
<td>0.01-0.1</td>
<td>20-20</td>
<td>30-60</td>
</tr>
<tr>
<td>LTG</td>
<td>0.5-0.77</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>ZNS</td>
<td>0.41-1.83</td>
<td>63</td>
<td>61-115</td>
</tr>
<tr>
<td>TPM</td>
<td>0.08</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>CBZ</td>
<td>0.5-2.5</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>LEV</td>
<td>0.8-1.3</td>
<td>6-9</td>
<td>16-19</td>
</tr>
</tbody>
</table>

* Use with caution, AAP.

Lamotrigine Excretion into Breastmilk

- N= 30 women, 210 breast milk samples
- Mean milk/plasma ratio was 41.3% [95% CI: 33.0%-49.9%]
- Infant conc. were 18.3% [9.5%-27.0%] of maternal plasma conc.
- Theoretic infant LTG dose was 0.51 mg/kg/day
- Relative infant LTG dose was 9.2%
- No adverse events noted, except mild thrombocytosis


Therapeutic Guidelines for Women on AEDs During Pregnancy

- Should include differential risks of AEDs, and ....
- How to optimize AEDs during pregnancy for best maternal and fetal outcomes
  - Consideration of number of AEDs and amount of AEDs
  - Is dose a surrogate marker for in utero fetal exposure
  - Role of therapeutic drug monitoring
- How to optimize use of AEDs during lactation
Maternal Outcomes & Neurodevelopmental Effects of Anti-Epileptic Drugs

Prospective, observational study, across 19 clinical sites

Pregnant Women with Epilepsy (n=350), compared to 2 control groups

- Pregnant healthy controls (n=100)
- Non-pregnant WWE (n=100)

Maternal Outcomes (Seizures, OB complications, Depression)

Children Outcomes (Neurodevelopment, Neonatal complications, Breastfeeding)

With PK modeling for level of exposure, with pharmacogenetic component

Multiple-PIs: Kimford Meador, MD (Stanford)
Perry B. Pennell, MD (BWH)

Obstetrics Core: Thomas McElrath, MD (BWH)
Maurice Druzin, MD (Stanford)

Neonatal Core: Linda Van Marter, MD (BWH)

MONEAD Study
Maternal Outcomes & Neurodevelopmental Effects of Anti-Epileptic Drugs

Funded by NIH/NINDS, NICHD #U01-NS038455-11A1

Perry Natal Case Hx revisited

- Pregnancy Hx:
  - LTG PP toxicity w/ ataxia, 45 mins – 2 hours post-dose: LTG level = 19
- Recent LTG levels: 6 – 12 μg/mL
- Current meds: LTG 200 BID, folic acid 4 mg QD
- Nonviable pregnancy dx, had D&E
- Re-establish LTG target concentration = 4-8 μg/mL
- Lowered Daily Dose to 300 mg and obtained pc baseline (6.2 μg/mL)

- February 2013: 41 yo, G 6P3, 7 2/7 weeks EGA, EDD 9/21/13
  - TDM plan started: Break-through seizure at 19 weeks EGA

Perry Natal Case Hx, continued

- 4/15/13: Boston Marathon bombing, multiple hospital lockdowns and evacuations, and oldest daughter undergoing ambulatory EEG, unable to return to CHB, forgot to call to follow-up LTG level
- 5/03/13: In Connecticut at restaurant: saw a flashbulb, then could not respond, drooling, had to be held up to not fall from sitting, went to Yale ER, UTI dx
- Began TDM every two weeks, with new target concentration = 6-10 μg/mL

Impact on Clinical Care & Practice

- Preconception
  - Transition to AED with favorable teratogenic profile
  - Establish individual target concentration
  - Lower dose as needed, with adjustment after D/C of any hormonal contraceptives
  - Use XR formulation and BID dosing if possible

- Pregnancy
  - Monthly AED levels for therapeutic drug monitoring
  - Adjust dose for seizures, SEs, and to maintain RTC > 0.65

- Postpartum
  - Adjust dose to (slightly above) pc baseline in 2 weeks - 3 months, depending on AED
  - Educate about newborn care and importance of sleep
  - Breastfeeding plan when desired
  - Educate about clinical signs of medication toxicity
Thank you for your attention!
Management of Seizures in HIV+ Patients
December 7, 2013
Gretchen L. Birbeck, MD MPH DTMH
University of Rochester, Rochester

Learning Objectives

• Gain new insights into how individual data on HIV virus profiles is used to inform care
• Recognize key complexities in providing care for seizures in persons with HIV
  • AED/ARV interactions
  • HIV-associated comorbidities relevant to seizure mgmt

Data on an individual’s HIV virus profile informs personalized care

Anticipate AED/ARV interactions

• Except in resource-limited settings, ARVs are now recommended for all HIV+ individuals
• Must assume that when you treat someone who is HIV+, they are or will be soon on ARVs

Guidelines

• Genotype resistance is recommended at baseline and, if ARVs are deferred, should be repeated prior to ARV initiation
• Needed given 20 different ARVs which need to be combined into 3- to 4-drug regimen
e.g. NNRTIs’ low genetic barrier for the development of resistance. High level resistance to all NNRTIs occurs with a single mutation and cross resistance is common

NNRTI=non-nucleoside reverse transcriptase inhibitor
Standards or ARV Naïve Patients

• efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC)
• ritonavir-boosted atazanavir + tenofovir disoproxil fumarate/emtricitabine (ATV/r + TDF/FTC)
• ritonavir-boosted darunavir + tenofovir disoproxil fumarate/emtricitabine (DRV/r + TDF/FTC)
• raltegravir + tenofovir disoproxil fumarate/emtricitabine (RAL + TDF/FTC)

2 NRTIs + 1 NNRTI

Factors for selecting ARVs

• Comorbidities
• Potential AEs
• Drug interactions
• Pregnancy potential
• Resistance per genotype
• Pre Rx HIV viral load
• Gender and pretreatment CD4 for NVP
• HLA-B*5701 for ABC
• Coreceptor tropism for MVC
• Patient preference
• Adherence potential

HIV Treatment: ARV selection

• Based upon sequence analysis of HIV genome providing estimates of drug susceptibility from the mutational patterns detected
• Computer-aided genotype interpretation systems (GIS) comprising rules developed from in vitro and in vivo resistance data
• GIS learn from the large data sets of patient histories and can provide accurate estimate of probable virological response to different ARV regimens.

Genotype Interpretation Systems

• Genotype interpretation systems are updated regularly based upon
  (1) in vitro drug susceptibility (phenotype)
  (2) patient treatment history
  (3) in vivo response to therapy.

HIV Resistance Response Database Initiative (RDI)

• First attempt to build a large international repository of genotype response data and exploit sophisticated data mining techniques to predict treatment outcome

HIV RDI

• The RDI (free online tool) uses artificial neural networks and random forest models to predict the absolute viral load change following treatment switch for a given HIV genotype
  • www.hivrdi.org
EuResist

• Collects data from multicentric HIV clinical databases in Europe
• Sources are regularly updated and the physically integrated EuResist database is periodically refreshed.
• Data include the demographics, viral loads, CD4 counts, treatment history and HIV genotypes for ~49,000 patients.
• From these, instances of treatment change episode are derived that inform the models

Evaluating the Patient’s Genome

• Recommendations advise screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR)
• HLA-B*5701-positive patients should not be prescribed ABC
• The positive status should be recorded as an ABC allergy in the patient’s medical record

Complexities of Seizure Management in HIV+ Patients

AED-ARV Interactions

• Cobicistat (COBI) is a potent CYP 3A inhibitor and will increase the concentration of other drugs metabolized by this pathway

AED-ARV Interactions

• SAQUINAVIR/RITONAVIR (SQV/r) is not recommended in patients with pretreatment QT interval >450 msec. Avoidance with ARVs that impact cardiac conduction may be prudent (e.g. Ezogabine)
Absolutes

• Rilpivirine (RPV) and etravirine (ETR) are contraindicated with carbamazepine, oxcarbazepine, phenobarbital, phenytoin
• Most ARVs with oral midazolam – Single dose IV with monitoring can be considered

AEDs with Protease Inhibitors

<table>
<thead>
<tr>
<th>PI</th>
<th>CBZ boosted PI:</th>
<th>DRV/R CBZ increased</th>
<th>Monitor AED levels and viral load</th>
<th>NVP possible increased DRV possibly decreased Monitor alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV</td>
<td>ATV (PPI): LPV (QD); SQV</td>
<td>ATV increased</td>
<td>Monitor AED levels and viral load</td>
<td>Monitor for ATV toxicity</td>
</tr>
<tr>
<td>RTV</td>
<td>FV possible decreased</td>
<td>Monitor AED levels and viral load</td>
<td>Monitor for ATV toxicity</td>
<td></td>
</tr>
<tr>
<td>SQV</td>
<td>FV possible decreased</td>
<td>Monitor AED levels and viral load</td>
<td>Monitor for ATV toxicity</td>
<td></td>
</tr>
<tr>
<td>TPV</td>
<td>FV possible decreased</td>
<td>Monitor AED levels and viral load</td>
<td>Monitor for ATV toxicity</td>
<td></td>
</tr>
</tbody>
</table>

AEDs with NNRTIs

<table>
<thead>
<tr>
<th>AED</th>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>Decreased AED and EFV possible</td>
<td>DO NOT USE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>Decreased AED and NVP possible</td>
<td>Monitor AED and EFV levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>Decreased RPV possible</td>
<td>DO NOT USE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AEDs with Integrase Inhibitors

<table>
<thead>
<tr>
<th>AED</th>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>EVG+COBI/TDF/FTC CBS</th>
<th>EVG+COBI/TDF/FTC ETX</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>Decreased MCV possible</td>
<td>If used without a strong CYP3A inhibitor; use MCV 600 mg BID or an alternative AED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>Decreased MCV possible</td>
<td>Use another benzo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>Decreased MCV possible</td>
<td>Use another benzo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C-C Chemokine Receptor Type 5 (CCR5) Antagonists

<table>
<thead>
<tr>
<th>AED</th>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Decreased MCV possible</td>
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<td></td>
<td></td>
</tr>
</tbody>
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ARVs with Benzos

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<th>AED</th>
<th>Dosage</th>
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### ARV Side Effects

- EFV causes CNS adverse effects (abnormal dreams, dizziness, headache, and depression) and lowers the seizure threshold
- To varying degrees, ARVs can cause or worsen hepatic dysfunction
- PIs cause dyslipidemia and insulin resistance which may already be problematic in individuals exposed to long term EI-AEDs
- PIs associated with nephrolithiasis
  - Avoid with zonisamide and topiramate?

### ARV Side Effects

- NRTIs can cause mitochondrial dysfunction and lactic acidosis
  - Avoid in individuals with mitochondrial dysfunction or epilepsy syndromes associated with mitochondrial dysfunction
  - Avoid with topiramate?

### Summary

- Avoid EI-AEDs and ARVs
- Avoid VPA and ETX with ARVs
  - Monitor for toxicity
- Follow LTG levels
  - Benzos + ARVs are problematic
    - Lorazepam
    - Oxazepam
    - Temazepam
  Best options but still require close monitoring and should be for inpatient (preferably ICU) usage
AET Symposium 2013:
One size does not fit all:
Personalized Medical Care
December 7th, 2013
Co-chairs:
Aristea S. Galanopoulou, MD PhD
Albert Einstein College of Medicine, Bronx NY USA
Angus A. Wilfong, MD
Baylor College of Medicine, Houston, TX USA

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Up To Date

Learning Objectives from the AET symposium
• Develop a rational approach for the selection of the optimal antiepileptic formulation and delivery system for each individual patient with resulting increased adherence, efficacy and tolerability.
• Recognize early adverse drug reactions and the patient populations at risk for developing them and implement treatment protocols that minimize such adverse outcomes.

Management of Epilepsy
• Our patients will likely be taking the drug we choose for a very long time, perhaps a lifetime.
  • Choose the very best drug first; the first drug used is the most efficacious
  • There are many changes ahead for our patients taking this drug
    • Maturation, pregnancy, concomitant medications, comorbidities

Management of Epilepsy
• Genes and genetic heritage are major determinants of medication efficacy, safety, and tolerability – choose your parents carefully
  • Pharmacogenetics and genomics is upon us
  • Standard of care to perform genetic analysis in many epilepsy syndromes – helps to predict efficacy (SCN1A) and safety (HLA-B*1502)
**Case 1:**
A 20 year old girl of Chinese descent is brought to the emergency room by EMS, because of an episode of convulsive seizure.

Her parents report that at 2am they were awakened by a noise in the patient's room. The patient was found shaking bilaterally, with asymmetric tonic posturing of the right arm.

EMS arrived at 2:15am, when the patient was postictal. A second seizure was observed at 2:20am and lorazepam was given IV at 2:25am.

The seizure resolved after this and the patient gradually returned to baseline while at the ER.

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**Case 1 (cont’d):**

**PMH:**
- A similar nocturnal event occurred 2 weeks prior to this ER admission.
- Last menstrual period: 2 months ago
- Recent loss of weight (3kg in 2 weeks) with nausea, vomiting in the morning and mild frontal headaches. No history of fevers.

**FH:** Her mother and grandmother had epilepsy, both with nocturnal seizures.

**SH:** Sexually active, boyfriend was ex-IVDU, no precautions.

**Meds:** None taken so far.

**Allergies:** None known.

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**Case 2:**

6 month old boy is referred to the EMU for evaluation of daily clusters of head drops and occasional body flexion, starting 2 weeks prior to admission.

- On exam he has 3 white patches on his skin; can track past midline; cannot roll over yet, has some head lagging.
- Video-EEG reveals infantile spasms.
- MRI of brain is scheduled but not available at the time.

**PMH:** Birth history was unremarkable.

**FH:** First born son. The parents do not report FH of seizures or other neurological problems. The mother has facial angiofibromas.

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**Case 3:**

6 month old baby girl had her first febrile seizure at 5pm:
- Temp 100.5°F.
- Clonic seizure on the right, for 10min.
- Postictal at the time of EMS arrival (5:20pm)

- 5:40pm: A second seizure on the way to the ER:
  - Clonic seizure mostly on the left
- 5:45pm: rectal diazepam was given by EMS, seizure resolves.
- 6pm: Arrival at the ER, postictal, gradually returns to baseline. Exam unremarkable.

**PMH:** Birth history was unremarkable. No prior history, normal development.

**FH:** First born child. No FH of seizures reported.

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**Case 1: Questions**

- Which antiseizure medication to start?
  - Not Carbamazepine without HLA testing!
- What formulation?
  - Optimally one to maximize adherence – 10% daily
- Can we predict toxicity / tolerability / allergic reaction?
- HLA genetic testing
- Are any concerns for comorbid or associated conditions?
  - What if the patient is pregnant?
  - What if she is HIV+?
  - Planned pregnancies (contraception), AED:ARV interactions
- Are any additional considerations for the future medical management of this patient?
  - Consideration of AED weaning, next AED if AEs or seizures.

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**Case 2: Questions:**

- Which medication to start?
  - Likely dx of TSC – consideration for Vigabatrin as first line
- Which formulation?
  - Maximize adherence – parental convenience
- Can we predict toxicity / tolerability / allergic reactions?
  - Treatment emergent, trial and error
- Are any concerns for comorbid conditions?
  - TSC – monitor for SEGAs and AMLs
- Are any considerations for the future management?
  - Everolimus (mTOR modulator) indicated for SEGAs and AMLs, clinical trials completed and on-going in epilepsy
Case 3: Questions

- Any considerations for the future management?
  - Is recurrence likely? Yes, focal ss's with low temp elevation
  - Is rescue medication indicated for future seizures and what are the preferred formulations? Yes. Maximize adherence
  - Can we predict recurrence / outcome? Genetic testing may define phenotype (SNCN1A)
- If our patient develops afebrile seizures, is there any diagnostic / genetic workup that may provide:
  - Syndromic classification? Dravet’s syndrome
  - Prognostic information, including for treatment response
    Avoid “sodium channel” AEDs
  - Predict toxicity / adverse reactions?
    Treatment emergent, trial and error

ARS Question 1
Choose the CORRECT answer.

In the acute treatment of seizures:
A. Time to seizure cessation after dosing is faster with intranasal midazolam than with IV diazepam
B. Time to seizure control after decision to treat has been consistently found to be shorter for IV diazepam than buccal midazolam
C. IM midazolam stops seizures faster than IV lorazepam due to shorter time of drug preparation and delivery
D. In the prehospital treatment of status epilepticus, IV lorazepam is more effective than IM midazolam in terms of proportion of patients arriving to the ER free from seizures without rescue therapy

ARS Question 2
Choose the WRONG answer.

When treating an HIV+ person with epilepsy, it is important to consider:
A. Genotype resistance, prior to selection of an antiseizure drug
B. Monitoring Valproic acid (VPA) levels, virologic response, and Lopinavir/ritonavir (LPV/r) related toxicities
C. Avoiding antiseizure drugs that affect cardiac conduction (e.g., Ezogabine) with Saquinavir/r
D. Avoiding oral midazolam with most antiretrovirals

ARS Question 3

Which of the following AEDs does not reduce efficacy of oral contraceptive pills?
A. Phenotyin
B. Valproic acid
C. Carbamazepine
D. Topiramate
E. Oxcarbazepine

ARS Question 4

JS is a 32yo woman with TLE well-controlled on lamotrigine monotherapy and a combined oral contraceptive pill. She is planning to stop her birth control and try to conceive. What else can you do to further improve her chance of a healthy outcome for her and her unborn child?
A. Reinforce use of folic acid beginning prior to conception
B. Obtain a baseline LTG level now
C. Adjust LTG dose prior to conception to <300 mg per day if possible; lower dose after COC is D/C
D. Obtain preconception LTG level on new dose without COC
E. All of the above

ARS Question 5
Choose the WRONG answer:
A. Morbilliform rashes are never drug-induced
B. Risk factors for drug reactions include: female gender, increasing age, number of drugs, immunosuppression
C. Leukocytoclastic vasculitis can be caused by phenytoin
D. Acute generalized exanthematous pustulosis can be caused by carbamazepine