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

Hot Topics Symposium
Epilepsy Updates

Symposium Chair:
Michael Sperling, M.D.

Tuesday, December 8, 2015
Convention Center – Room 201

8:45 – 10:45 a.m.

GENERAL INFORMATION

Accreditation

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

Credit Designation

Physicians

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

Physician Assistant

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

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

Nursing

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

This activity is awarded 30.75 contact hours.

Nurse Practitioners

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

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

Pharmacy

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

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

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

International Credits

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

CME/CE Certificates

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

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

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

Attendance Certificate/International Attendees

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

Policy on Commercial Support and Conflict of Interest

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

Disclosure of Unlabeled/Unapproved Uses

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

OVERVIEW
This program will provide information to enable physicians and other health care providers to improve diagnostic and patient management skills. The topics include practical approach to ordering and interpreting genetic testing for epilepsy, a practical approach to diagnosing and treating autoimmune epilepsy, a review of indications and use of valproate for women with epilepsy and an update on cannabis and cannabinoid use in epilepsy.

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

- Utilize diagnostic testing for genetic and autoimmune disorders more effectively, to better diagnose and treat these conditions
- Prescribe valproate more effectively to improve medical management of women with epilepsy
- Discuss the latest information regarding cannabis and epilepsy to provide better advice for patients

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

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Chair: Michael Sperling, M.D.

Introduction
Michael Sperling, M.D.

When Should Genetic Testing Be Performed?
Annapurna Poduri, M.D.

When Should Autoantibody Testing Be Performed?
Christian Bien, M.D.

Should Valproate be Prescribed to Women and Girls of Childbearing Potential?
Torbjörn Tomson, M.D., Ph.D.

Cannabis Update
Kelly Knupp, M.D.

Conclusions
Michael Sperling, M.D.

Education Credit
2.0 CME Credits

Nurses may claim up to 2.0 contact hours for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.0 contact hours (0.2 CEUs). UAN 0077-9999-15-040-L01-P. Initial Release Date: 12/8/2015.

The American Board of Psychiatry and Neurology has reviewed the Hot Topics Symposium: Epilepsy Updates and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

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
Michael Sperling, M.D. (Chair)
Dr. Sperling is Baldwin Keyes Professor of Neurology at Thomas Jefferson University in Philadelphia, where he is also Vice Chair for Clinical Affairs of the department of Neurology,
Director of the Jefferson Comprehensive Epilepsy Center and Clinical Neurophysiology Laboratory, and Director of Clinical Research. He has published nearly 300 peer reviewed articles, book chapters, and reviews and 2 textbooks related to epilepsy. He is actively engaged in epilepsy and cognitive neuroscience research, and lectures widely about these topics. He presently serves as an editor-in-chief of Epilepsia.

Dr. Sperling discloses receiving support as Contract Researech from NIH, DARPA, UCB Pharma, Eisai, Sunobion, SK Life Sciences, Glaxo, Upsher-Smith, Acorda, Medtronics, Marinus, Brain Sentinel, Pfizer (all payments to Thomas Jefferson University); Other Services member of Board of Directors of the Epilepsy Foundation of Eastern PA, Editor in Chief of Epilepsia, member of the ILAE Executive committee.

Christian Bien, M.D.
Prof. Dr. Christian G. Bien is the Clinical Director of Krankenhaus Mara, Epilepsy Center Bethel, Bielefeld/Germany. He obtained his Medical Degree from the Free University of Berlin and completed his neurology training at the Medical Center of the University of Bonn. His main fields of clinical and research activities are autoimmune epilepsies and presurgical assessment of drug-resistant epilepsy patients. He runs a lab for determination of antineural antibodies at his hospital.

Dr. Bien discloses receiving support for Royalties from My employer (Krankenhaus Mara, Bielefeld, Germany) runs a laboratory for the detection of auto-antibodies; external senders are charged for antibody diagnostics.; for Consulting from Eisai (Frankfurt, Germany) and UCB (Monheim, Germany); for Speakers Bureau from Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany); for Contract Research from Astellas Pharma (München, Germany), Octapharma (Langenfeld, Germany), diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany); for Honoraria from Eisai

(Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany).

Dr. Bien does intend to reference unlabeled/unapproved uses of drugs or products - Prednisolone, methylprednisolone, rituximab, cyclophosphamide, intravenous immunoglobulins (all for therapy of autoimmune epilepsy).

Kelly Knupp, M.D.
Kelly Knupp received her MD from the University of New Mexico - School of Medicine. She completed her residency in Pediatrics at Children's Hospital of New York followed by Pediatric Neurology Residency at Columbia University at Children's Hospital of New York. After her residency, she trained as a Clinical Fellow in Pediatric Epilepsy at the Columbia Comprehensive Epilepsy Center at New York Presbyterian Hospital. Dr. Knupp now practices at Children's Hospital Colorado in Aurora, CO and is Associate Professor of Pediatrics and Neurology at the University of Colorado. She is the Director of the Dravet Program.

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

Annapurna Poduri, M.D.
Annapurna Poduri, MD, MPH is a physician-scientist with a focus on epilepsy genetics. She is an Associate Professor in Neurology at Harvard Medical School and serves on the faculty of Boston Children's Hospital Department of Neurology, where she directs the Epilepsy Genetics Programs. She studies the genetics of brain malformations and early onset epilepsy, and her team is modeling epilepsy genes in the zebrafish system. She is active in "team science" through the Epilepsy Phenome/Genome Project, Epi4K, and the Epilepsy Precision Medicine consortia. She has recently been awarded the Dreifuss-Penry Epilepsy Award from the AAN and the Derek Denny-Brown Neurological Scholar Award from the ANA.

Dr. Poduri discloses receiving support for Contract Research from Marinus ganaxalone study for PCDH19 (funds to institution).

Torbjörn Tomson, M.D., Ph.D.
Torbjörn Tomson, MD, PhD, FRCP Edin, Professor of Neurology and Epileptology at the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, and consultant neurologist at Karolinska University Hospital. Honorary Professor at Hanoi Medical University. Serves since 1999 as chair of EURAP, the International Antiepileptic Drugs and Pregnancy Registry. Member of the ILAE Commission on European Affairs.
Dr. Tomson discloses receiving support for Consulting from Eisai and UCB for participation in advisory board (paid to my institution); as Contract Research from Grants to institution, not personal from GSK for case-control study of SUDEP, from GSK, Eisai, UCB, Novartis and Bial for EURAP, International Pregnancy Registry; for Honoraria from BMJ Education India, lecture honoraria; as Other Service from Associate editor of Epileptic Disorders, Chair of ILAE publication Task Force.

CME Reviewer
Kevin Chapman, M.D.
Dr. Chapman is a Pediatric Epileptologist at the University of Colorado at Denver and Children's Hospital Colorado.

Kevin Chapman, M.D. discloses receiving support as Contracted Research local PI for the Insys CBD trials on Dravet and LGS at UC Denver. All funds go to my department.

Lara Jehi, M.D.
Dr Lara Jehi is an adult epileptologist, the head of the Outcomes Research Program, and the Director of Research at the Cleveland Clinic Epilepsy Center. Her interests have focused on understanding and improving outcomes of epilepsy treatment. She 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, is serving in leadership roles on many educational committees within the American Epilepsy Society and American Academy of Neurology, and is a reviewer for the Epilepsy Study Section at NIH. She has authored several original manuscripts, editorials and book chapters and spoke at multiple national and international meeting.

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

Jack Lin, M.D.
Dr. Jack Lin is an Associate Professor and the Director of the Comprehensive Epilepsy Program at the University of California, Irvine. Using advanced neuroimaging techniques, his research has uncovered neurodevelopemental impacts of new-onet pediatric epilepsies, examined brain network alterations associated with mood disorders in temporal lobe epilepsy, and delineated relationships between brain structural changes and cognitive deficits in a wide range of epilepsy syndromes. He serves as a a grant reviewer for the Epilepsy Foundation, an Ad hoc reviewer for many journals, a member of editorial board of Epilepsy and Behavior, member of several committees at the American Epilepsy Society

Dr. Lin discloses receiving support as Speakers Bureau from UCB and Sunovion Pharmaceuticals.

Coutrney Wusthoff, M.D.
Dr. Wusthoff is Assistant Professor of Child Neurology and by courtesy, Pediatrics (Neonatal and Developmental Medicine) at the Stanford University School of Medicine. She is also Neurology Director for the Lucile Packard Children's Hospital Stanford Neuro-NICU. She conducts clinical research in neonatal neurology, focusing on neonatal seizures, critical care EEG monitoring, and early onset epilepsies. Her clinical work includes inpatient and outpatient neonatal neurology, clinical neurophysiology, and pediatric epilepsy care.

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

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

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

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

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

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

AKH staff and planners have nothing to disclose.

CLAIMING CREDIT:

PHYSICIANS

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

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

How to Claim CME Credit

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

Questions?

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

NURSING & PHARMACY

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

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

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

WWW.AKHCME.COM/2015AES

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

DISCLAIMER

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

When should genetic testing be performed in epilepsy patients?

Annapurna Poduri, MD, MPH
Boston Children's Hospital
Epilepsy Genetics Program
Harvard Medical School

December 8, 2015

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

Disclosure

none

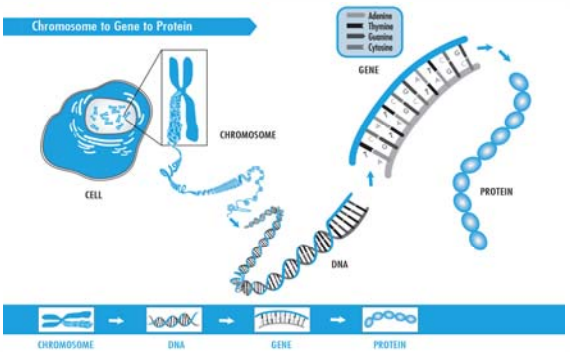
Learning Objectives

- To understand the status of epilepsy genetics in 2015
- To identify which patients should have testing
- To develop a rational approach to genetic testing in epilepsy

Impact on Clinical Care and Practice

- Diagnostic certainty
  - Prognosis, screening for non-neurological issues
  - End of diagnostic odyssey
- Possible change in medical management of epilepsy
  - Small but growing number of genes associated with specific treatment recommendations
  - Genetic diagnosis may influence consideration of epilepsy surgery vs. continuing medical therapy

Modern Genetics 101



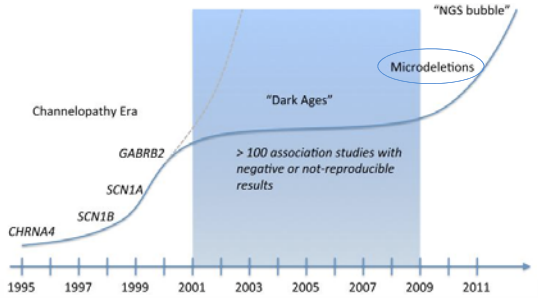
Emerging evidence for a role of genetics in epilepsy

- Twin studies
  - MZ>DZ concordance
- Family studies—increased risk to siblings
  - Generalized epilepsy 10%
  - Focal 5%
- Animal models of epilepsy
- Phenotypic Studies: Families with inherited epilepsy syndromes (e.g., GEFS+)

↓

- Genetic studies: linkage analysis, positional cloning →gene discoveries

Evolution/Explosion of Epilepsy Genetics

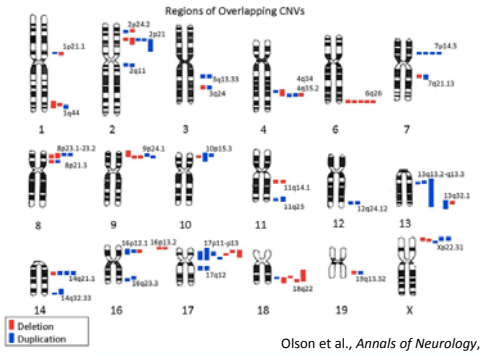


Role of CNVs in Epilepsy without an identified etiology

- 1234 cases with IGE
  →2% microdeletions, most **15q11.2** and **16p13.11**
- 517 case with IGE or focal epilepsy
  →3% deletions at **15q11.2**, **15q13.3**, or **16p13.11**
- 3812 cases with a range of epilepsies:
  →23 had **16p13.11** deletions (100 kb or larger)

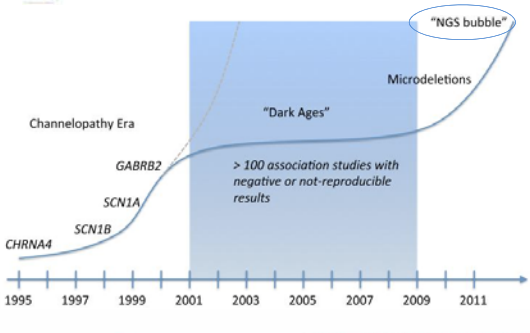
Heinzen et al., Mefford et al., de Kovel et al., 2010

Microdeletion/microduplication syndromes and epilepsy (805 cases, ~5% yield)



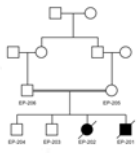
Olson et al., *Annals of Neurology*, 2014

Evolution/Explosion of Epilepsy Genetics



Complex landscape of epilepsy genetics

inherited mutations

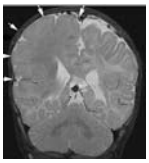


Autosomal Dominant
-heterozygous
Autosomal Recessive
-homozygous
-compound heterozygous

de novo mutations

Heterozygous

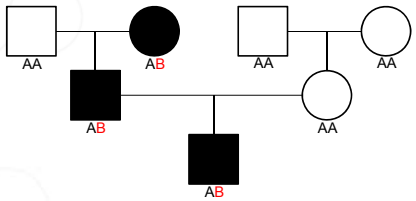
de novo post-zygotic mutations



Heterozygous
-typically mosaic

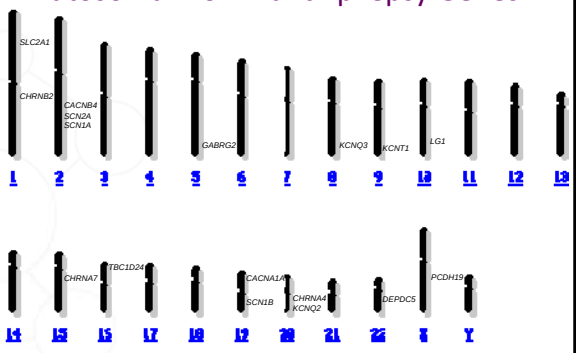
Autosomal dominant inheritance in epilepsy

Example: Autosomal dominant partial epilepsy with auditory features
B= *LGI1* heterozygous mutation



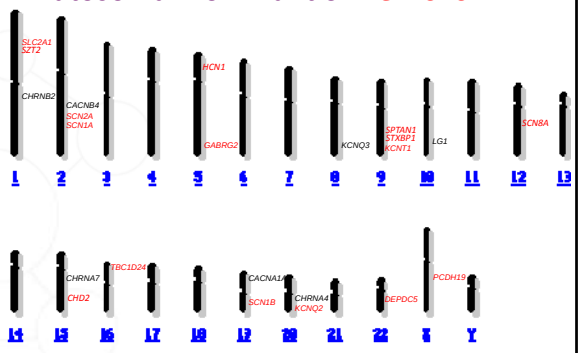
A=not associated with disease, most common allele in the population
B=disease-associated allele

Autosomal Dominant Epilepsy Genes



Poduri and Lowenstein, *Curr Opin Genet Dev* 2011

Autosomal Dominant or *De Novo*



Poduri and Lowenstein, *Curr Opin Genet Dev* 2011

De novo Mutations in Cohorts with Early Onset Epilepsies

- 264 trios with infantile spasms and Lennox-Gastaut syndrome

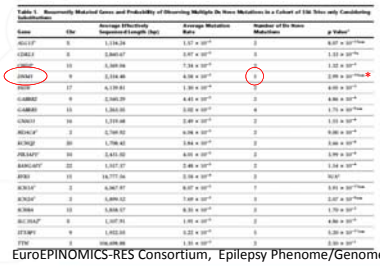
Table 1 | Probability of observing the reported number of *de novo* mutations by chance in genes recurrently mutated in this cohor

Gene	Chromosome	Average effectively captured length (bp)	Weighted mutation rate	De novo mutation number	P value†
SCN1A	2	6,063.70	1.61×10^{-5}	5‡	1.12×10^{-13} *
STXBP1	9	1,917.51	6.44×10^{-5}	5	1.16×10^{-11} *
GABRB3	15	1,206.86	3.78×10^{-5}	4	4.11×10^{-10}
CDKL5	X	2,798.38	5.44×10^{-5}	3	4.90×10^{-7}
ALG13	X	475.05	1.03×10^{-5}	2	7.77×10^{-12}
DNM1	9	2,323.37	9.10×10^{-5}	2	2.84×10^{-6} ns
HCN1	2	2,649.82	1.16×10^{-4}	2	4.57×10^{-6}
SCN2A	2	5,831.21	1.52×10^{-4}	2	1.14×10^{-5}
SCN8A	12	5,814.48	1.64×10^{-4}	2	9.14×10^{-6}

Epi4K Consortium & Epilepsy Phenome/Genome Project *Nature*, 2013

De novo Mutations in Cohorts with Early Onset Epilepsies

- Expanded effort to 356 trios



EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, and Epi4K Consortium, *Am J Hum Genet*, 2014

De novo Mutations in Cohorts with Early Onset Epilepsies

- Expanded effort to 356 trios

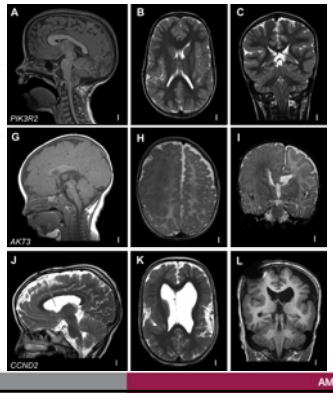
Table 1. Recurrently Mutated Genes and Probability of Observing Multiple De Novo Mutations in a Cohort of 356 Trios only Considering Substitutions

Gene	Chr	Average Effectively Sequenced Length (bp)	Average Mutation Rate	Number of De Novo Mutations	p Value*
ALG13‡	X	1,134.24	1.57×10^{-5}	2	8.07×10^{-12} **
CDKL5	X	2,860.67	3.97×10^{-5}	3	1.33×10^{-6} *
CHD2‡	15	5,369.04	7.34×10^{-5}	2	1.32×10^{-5}
DNM1	9	2,334.48	4.58×10^{-5}	5	2.99×10^{-10} ** *

Phenotype: Infantile spasms, onset between 2 and 13 months
4/5 → Lennox-Gastaut syndrome
Severe to profound intellectual disability (nonverbal)
Hypotonia

EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, and Epi4K Consortium, *Am J Hum Genet*, 2014

De Novo Post-zygotic Mutations



Megalencephaly
Polymicrogyria

Hemimegalencephaly

Megalencephaly
Polymicrogyria
Hydrocephalus

Which epilepsy patients should have genetic testing?

- Inherited epilepsy?
  - Example: 14-year-old young woman with juvenile myoclonic epilepsy and a family history of generalized epilepsy (mom) and febrile seizures (maternal aunt)
- Patients with syndromes resembling those associated with *de novo* mutations?
  - Example: 6-month-old boy with new-onset infantile spasms with hypsarrhythmia and negative MRI

Does it make a difference clinically?

- Diagnostic certainty/prognosis
  - IF the 14-year-old young woman with JME and + family history had a mutation in a gene always associated with a benign course→reassurance that it is non-progressive
  - IF the 6-month-old boy had a mutation in an "epilepsy gene," testing for possible metabolic testing (LP, etc.) could be stopped.
- Impact on treatment?
  - Specific genes→specific treatments to pursue/avoid
  - Future
    - Pharmacogenomic testing (HLA, CYP, etc.)
    - Precision medicine for some epilepsies

Which epilepsy patients should have genetic testing?

- Diagnostic certainty/prognosis
- Impact on treatment

SUMMARY of who should have genetic testing

- Diagnostic certainty: **"Epilepsy Plus" …**
  - Dysmorphic features
  - Intellectual disability/likely ID (infantile spasms, etc.)
  - Autism
- Impact on treatment: **Refractory epilepsy**
  - Early onset epileptic encephalopathy
  - Early onset absence (<4yo)
  - Familial focal epilepsy

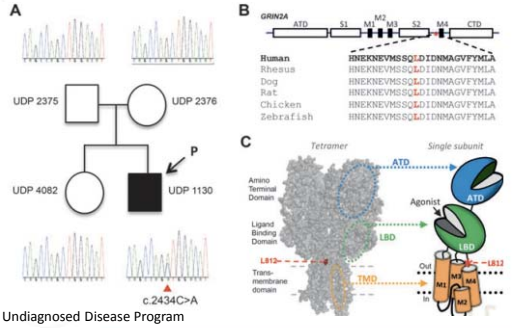
Genetic diagnoses that influence treatment

- *SCN1A*→avoid LTG and PHT (in general, not always)
- *SCN2A*→high-dose PHT helpful
- *SLC2A1*→ketogenic diet
- *ALDH7A1*→pyridoxine
- *PNPO*→pyridoxal-5-phosphate

- *KCNQ2*→consider ezogabine
- *KCNT1*→consider quinidine
- *GRIN2A*→consider memantine
- *TSC*→consider everolimus?
- Other mTOR-related epilepsies→everolimus?

OFF LABEL
NEED TO ESTABLISH MUTATION EFFECT
BEST THROUGH A CLINICAL TRIAL

GRIN2A L812M in a child with epileptic encephalopathy, tonic+myoclonic sz



NIH Undiagnosed Disease Program
Pierson et al., *Annals of Clinical Translational Neurology*, 2014

GRIN2A L812M and precision medicine

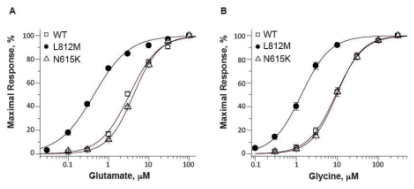
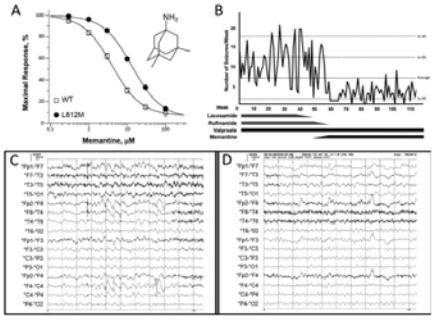


Figure 3. Functional analysis of GluN1/GluN2A receptors, GluN1/GluN2A-N615K receptors, and GluN1/GluN2A-L812M receptors. (A) The composite glutamate (in the presence of 100 μmol/L glycine) and (B) glycine (in the presence of 100 μmol/L glutamate) concentration-response curves indicate an increased agonist potency in GluN1/GluN2A-L812M compared to wild-type and GluN1/GluN2A-N615K NMDA receptors. Fitted EC_{50} values are given in μmol/L in the symbol legend.

GAIN-OF-FUNCTION MUTATION

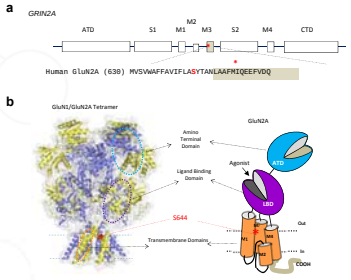
Pierson et al., *Annals of Clinical Translational Neurology*, 2014

GRIN2A L812M and precision medicine: Memantine reduces GluN2A response



Pierson et al., *Annals of Clinical Translational Neurology*, 2014

BCH patient with infantile spasms *GRIN2A* c.1930A>G, p.Ser644Gly

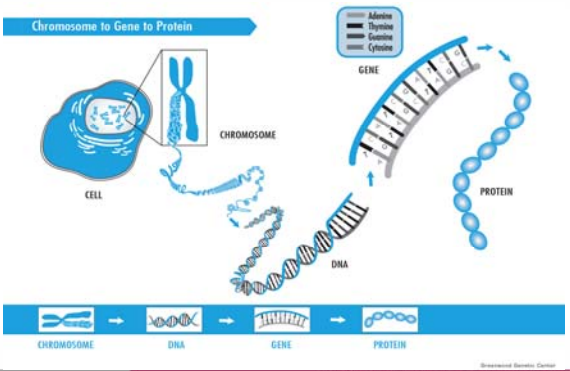


Jurriaan Peters, Heather Olson
Steve Traynelis (Emory)

When should testing should be done? What tests should be undertaken?

- Clinical data suggest a classic syndrome associated with one gene
  - Down syndrome→ karyotype for trisomy 21
  - Dravet syndrome→*SCN1A* sequencing, deletion, duplication
  - Rett syndrome→*MECP2* sequencing, deletion, duplication
- Clinical data suggest a syndrome category associated with several genes
  - Small number of treatable causes—but growing!
  - Genetic diagnosis may influence consideration of epilepsy surgery vs. continuing medical therapy

What is tested in genetic testing?



Approaches to testing

- The options
  - Chromosomal microarray analysis (CMA)
  - Single gene testing (seq/del/dup)
  - Panel testing (epilepsy panel, autism panel)
    - All have seq, only some have del/dup option
  - 'Whole' exome sequencing (WES)
- Phenotype highly suggests a specific syndrome
  - Testing for that syndrome
    - Dravet syndrome→SCN1A seq/del/dup
    - Angleman→CMA→if negative, *UBE3A* sequencing, possibly epilepsy panel for Angelman-like genes→if all negative WES since highly likely genetic
    - Early onset absence→*SLC2A1*, possibly CSF glucose

Approaches to testing

- The options
  - Chromosomal microarray analysis (CMA)
  - Single gene testing (seq/del/dup)
  - Panel testing (epilepsy panel, autism panel)
    - All have seq, only some have del/dup option
  - 'Whole' exome sequencing (WES)
- Epilepsy 'plus' or refractory epilepsy, esp. early onset
  - CMA and epilepsy panel (even if genetic ddx is a short list)
  - If negative→WES

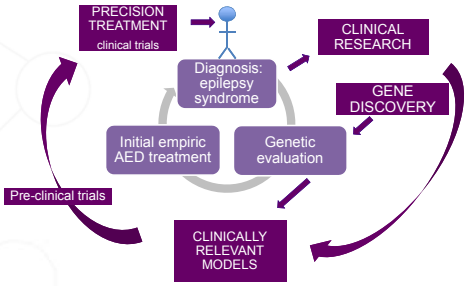
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

What if is all negative?

- Research options
  - Registry based on syndrome features (e.g., Dravet)
  - Individual research studies
  - Rare Epilepsy Network
  - Epilepsy Genetics Initiative (CURE, NINDS)

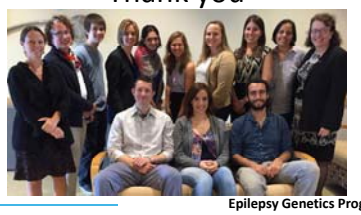
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

Can genetic testing lead us to PRECISION MEDICINE in EPILEPSY?



AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

Thank you



Epilepsy Genetics Program

Boston Children's Neurology Dept.
F.M. Kirby Neurobiology Center

Richard A. and Susan F. Smith President's Innovation Fund

Mark LaCoursiere Beth Sheidley Lacey Smith
McKenna Kelly Heather Olson Alex Jaksic
Michaela Meyer Becka Pinsky Christelle Achkar
Gessica Truglio Chris Yuskaitis

epilepsygenetics@childrens.harvard.edu

Translational Research Program

NIH National Institute of Neurological Disorders and Stroke

NINDS (K23, EPGP, Epi4K; Epilepsy Genetics Initiative with CURE)

Dravet Syndrome PCDH19 alliance The Cute Syndrome

#AESmtg15

AMERICAN EPILEPSY SOCIETY

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

When Should Autoantibody Testing Be Performed?

Christian G Bien, Epilepsy Center Bethel, Bielefeld/Germany

Bethel

December 08, 2015

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

Disclosure

CGB gave scientific advice to Eisai (Frankfurt, Germany) and UCB (Monheim, Germany), undertook industry-funded travel with support of Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Grifols (Frankfurt, Germany), obtained honoraria for speaking engagements from Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany), and received research support from Astellas Pharma (München, Germany), Octapharma (Langenfeld, Germany), diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany). His employer (Krankenhaus Mara, Bielefeld, Germany) runs a laboratory for the detection of auto-antibodies; external senders are charged for antibody diagnostics.

Learning Objectives

After this lecture, you should be able to …

- use the concept of "autoimmune epilepsy" clinically.
- identify patients in which antibody testing is worthwhile.
- order the appropriate tests.
- interpret antibody test results.

Autoimmune epilepsy

What is autoimmune epilepsy?

Autoimmune epilepsy

The ILAE suggestion

1) Genetic
2) Structural
3) Metabolic
4) **Immune**
5) Infectious
6) Unknown

Immune. A range of immune epilepsies has been recently recognized with characteristic presentations in both adults and children. An immune etiology can be conceptualized as where there is evidence of autoimmune-mediated central nervous system inflammation. Diagnosis of these autoimmune encephalitides is rapidly increasing, particularly with greater access to antibody testing. Examples include anti-NMDA receptor encephalitis and anti-LGI1 encephalitis. With the emergence of these entities, this etiological subgroup deserves a specific category particularly given the treatment implications with targeted immunotherapies.

Revised organisation and terminology of the epilepsies, proposal 10/2013. www.ILAE.org

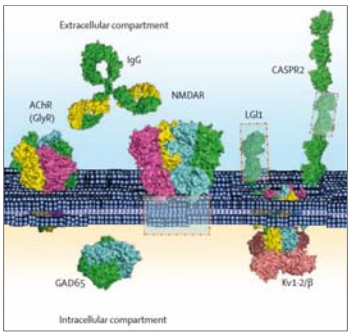
Autoimmune epilepsy

Preliminary remarks

- "Autoimmune epilepsy" is "Autoimmune encephalitis" *with a predominant epileptic phenotype*
- ≈80% of patients with autoimmune encephalitis have seizures/epilepsy
- ≈ 2% of all epilepsies have an autoimmune etiology (my personal estimate)

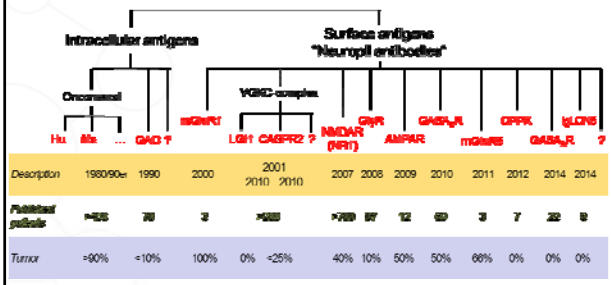
Irani SR et al., Curr Opin Neurol 2011;24:146

Autoimmune epilepsy
IgG antibodies and their antigens



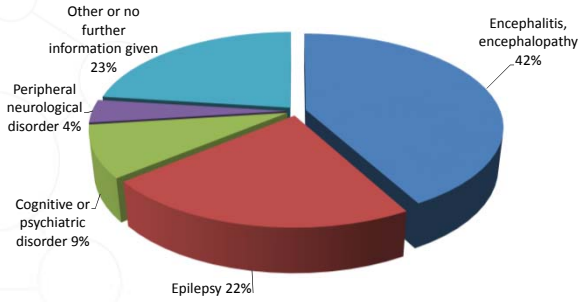
Vincent, Bien, Irani, Waters, Lancet Neurology 2011

Autoimmune epilepsy
The antigens



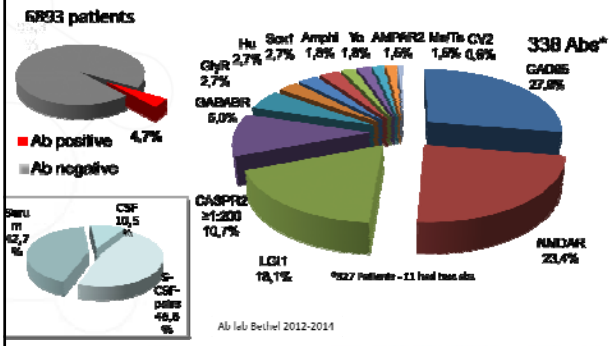
Description	1980/90er	1990	2000	2001 2010	2010	2007	2008	2009	2010	2011	2012	2014	2014
Published patients	>100	70	2	>100		>700	87	12	60	3	7	22	9
Tumor	≈90%	≈10%	100%	0%	≈25%	40%	10%	50%	50%	66%	0%	0%	0%

Suspected diagnoses of patients
Antibody lab Bethel, 300 consecutive patients



Dogan Onugoren M et al., JNNP 2015;86:965

Frequency of IgG antibodies
Antibody lab Bethel



Ab lab Bethel 2012-2014

Autoimmune epilepsy

When to suspect autoimmune epilepsy?

Autoimmune epilepsy
Suggestive features

"Syndrome":
- Limbic encephalitis
- Faciobrachial dystonic seizures
- Encephalopathy

Patient and history:
- Young females
- Other autoimmune conditions

Seizure types and patterns:
- Unexplained new onset epilepsy in adult life
- Onset with status or very high seizure frequency
- Pilomotor seizures

Paraclinical findings:
- EEG: "extreme delta brush"
- CSF: cell count ↑ or unmatched oligoclonal bands
- MRI: encephalitic lesion
- Histopathology: "chronic encephalitis"

Bien CG, Epilepsia 2013;54 Suppl 2:48

NMDAR antibodies
… and epilepsy in young ladies

- Females with new-onset epilepsy (<5 y) w/o obvious cause/syndrome (history, EEG, MRI)
- Manifestation between15 and 45 years of age
- Study period: 2½ y at a tertiary center (Bonn University)

➲ 19 patients identified
➲ 5/19 had NMDAR antibodies
➲ 4/5 had prominent psychiatric symptoms

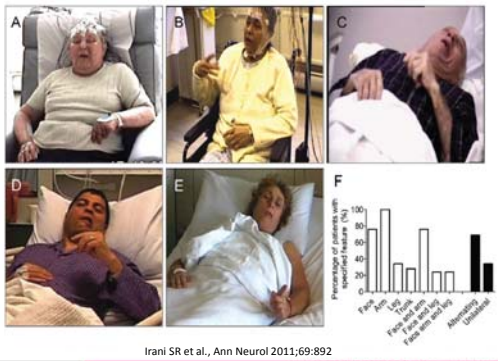
Niehusmann P et al., Arch Neurol 2009;66:458

Autoimmun-Epilepsie
Status epilepticus

- 13 patients from 8 centers with SE due to autoimmune encephalitis
- Antibodies to ….
  - NMDAR (N=8)
  - GAD (N=1)
  - Ri (N=1)
  - Neuropil (N=1)
  - No antibody found (N=2)
- Median duration: 2 months (2 h-12 y)
- Outcome as expected from the antibodies

Holzer FJ et al., Eur Neurol 2012;68:310

Faciobrachial dystonic seizures
Antibodies against VGKC complex/LGI1



Irani SR et al., Ann Neurol 2011;69:892

Faziobrachial dystonic seizures, LGI1 abs
E., P. 44 y ♀

Video

University of Bonn, Dept. of Epileptology

Autoimmune epilepsy
G., H. ♀ 66 y, LGI1 abs – 1 year after disease onset

Video

Epilepsy Centre Bethel

Autoimmune epilepsy
G., H. ♀ 66 y, LGI1 abs – 1 year after disease onset

Video

Epilepsy Centre Bethel

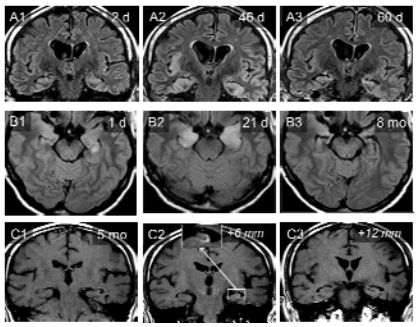
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

Autoimmune epilepsy
Suggestive features: Imaging (limbic encephalitis)

GABA$_B$R abs

AMPAR abs

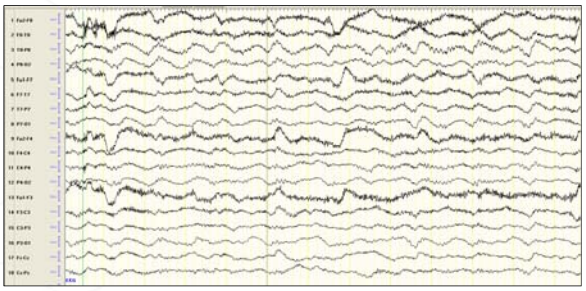
AMPAR abs



Dogan Onugoren M et al., J Neurol Neurosurg Psychiatry 2015;86:965

Autoimmune epilepsy
Suggestive features: EEG

O., N. ♀ 24 yrs, NMDAR (Nr1) abs: "Extreme delta brush"

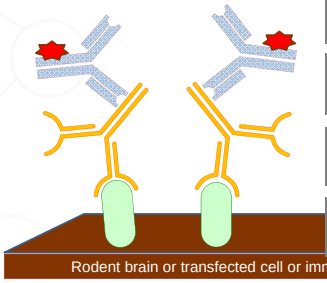


EEG from Epilepsy Centre Bethel. First description: Schmitt SE *et al.*, Neurology 2012;79:1094

Autoimmune epilepsy

What tests should be ordered?

Autoimmune epilepsy
Detection of IgG antibodies



Visualization molecule coupled to secondary ab (Fluorochrom or Avidin-Biotin-DAB)

"Secondary ab" from animal directed against human IgG

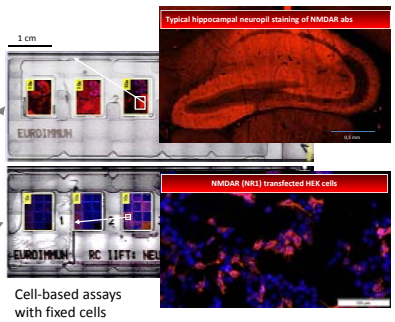
Antibodies from patient blood or CSF

Antigen, e.g. NMDAR oder LGI1

Rodent brain or transfected cell or immunoblot

Modifed from: Dogan Onugoren M et al., Z Epileptol 2015;28:196

Autoimmune epilepsy
Multiparametric testing for surface antibodies

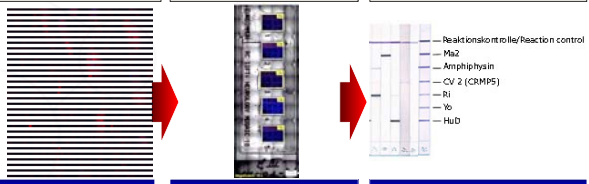


Cell-based assays with fixed cells

Antibody lab, Epilepsy Centre Bethel

Autoimmune epilepsy
Diagnostics for intracellular onconeural antibodies

Immunfluorescence | Cell-based assays | Immuno-Dot-Blot

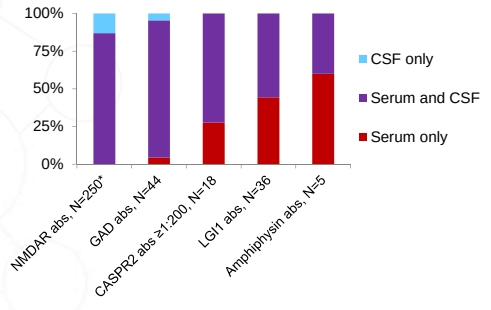


Search: Ma abs | negative | Confirmation: Ma2 abs

Mouse brain, mosaic assay: Euroimmun, Lübeck; Immunoblot: Ravo, Freiburg

Auto-antibodies

Serum or CSF? Data from Bethel Antibody Lab



*taken from Gresa-Arribas et al., Lancet Neurol 2014

Autoimmune epilepsy

What is a positive test?

Autoimmune epilepsy

Specific and responsive cases – gray cases

Case numbers

>100
20-99
10-19
<10

	N literature	Syndrome specificity	Specificity confirmed	Response to immuno-therapy
Specific and immuno-tx responsive cases: antibodies against …				
NMDAR i.L.		+	+	+
LGI1		+	+	+
CASPR2 ≥1:200 i.S.		+	+	+
AMPAR		+	+	+/-
$GABA_BR$		+	+	+/-
GlyR >1:50 i.S./i.L		+	(+)	+
DPPX		+	+	+/-
Gray cases: antibodies against …				
Onconeural ags (Hu…)		+	+	-
GAD65		+	+	-
VGKC-complex, not LGI1, CASPR2		+/-		+/-
$GABA_AR$		?		+/-
NMDAR (serum only)		?		
CASPR2 <1:200		-		?
GlyR<1:50 in serum		-		
mGluR5		?		?

Autoimmune epilepsy

What to do treatment-wise when the antibody test arrives?

Autoimmune epilepsy: treatment options

Our approach to patients with high-rank antibodies

All off-label

5*1 g IV-methlyprednisolone, then
80 mg prednisolone p.o. per day for 4 weeks

+/-

10 immunadsorptions

Re-evaluation (NMDAR abs: after 2 wks; other abs: ?)

Improvement

Taper prednisolone by 10 mg daily dose per week.

Deterioration

Steroids↑↑

Sustained improvement

Taper over 6 mo

No improvement

Rituximab, 4 times 375 mg/m² 1 week apart from each other (or 1 g twice, a fortnight apart)

and/or

Cyclophosphamide 750 mg/m² per month

Bien CG and Bien C, Z Epileptol 2015;28:201, based on Dalmau J *et al.*, Lancet Neurol 2011;10:63 and Irani SR et al., JAMA Neurol 2014;71:896

Autoimmune epilepsy: treatment options

Our approach in "gray cases"

All off-label

80 mg prednisolone p.o. per day for 4 wks.
Reduction by 10 mg/d per wk.#
When on 10 mg/d, i.e. **after 3 mo**:
Re-evaluation

#If steroids contraindicated: IVIG

No improvement

Discontinue immuno-tx

Partial improvement

Escalate immuno-tx e.g. more steroids, cyclophosphamide, rituximab …

Remission

Continue 5 mg prednisolone for another 6 months, then stop

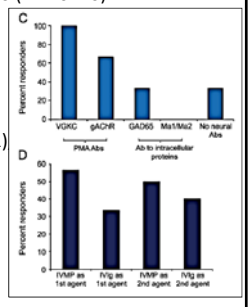
Bien CG and Bien C, Z Epileptol 2015;28:201

Autoimmune epilepsy: treatment options

Treatment-related outcome

- 30 pats, median epilepsy duration 12 mo (1-120 mo)
- 59% ≥2 AED
- 69% daily seizures
- Diagnosis based on
  - serum antibodies (79%) to LGI1 (12), CASPR2 (1), gAChR (3), GAD65 (6), Ma1/Ma2 (1) VGCC (1)
  - CSF abnormalities (69%)
  - MRI: encephalitic lesions (62%)
- Monthly MP or IVIG infusions, 6-12 wks

10 sz-free + 8 with ≥50% reduction (62%)



All off-label

Toledano M et al., Neurology 2014;82:1578

Autoimmune epilepsy

G., H. ♀ 66 y, LGI1 abs

Video

Epilepsy Centre Bethel

Autoimmune epilepsy

Final recommendations

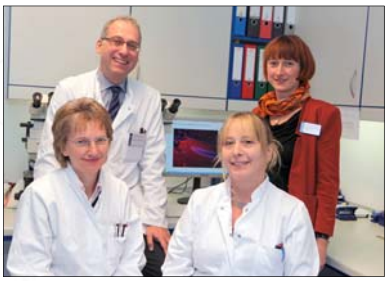
Autoimmune epilepsy

Final recommendations

- Testing of serum-CSF pairs recommended
- Specificity more important than sensitivity
- NMDAR abs in serum only, VGKC complex abs not directed to LGI1/CASPR2: questionable significance/specificity
- Non-IgG antibodies (IgM, IgA): no proven clinical significance
- Antibody-negative cases exist – treatability? Risk-benefit-ratio?
- Some antibodies promise very good seizure response to immunotherapies (e.g., LGI1, NMDAR)

Thanks to

Antibody lab Bethel



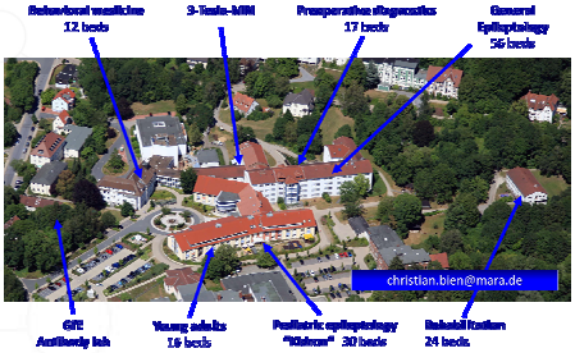
Dr. Corinna Bien

Dagmar Bonhaus-Liebmann

Jutta Potthoff

… und Prof. Dr. Theodor May, Society for Epilepsy Research, Bielefeld-Bethel

Epilepsy Centre Bethel: Krankenhaus Mara



Update on Valproate Prescribing for Women

Torbjörn Tomson, MD, PhD
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

Karolinska Institutet

December 8, 2015

1

Disclosure

Eisai, UCB	Honorarium to my department for Ad Board participation
GSK	Grant for SUDEP study
GSK, Eisai; UCB, Novartis, Bial	Grants for EURAP Pregnancy Registry
BMJ Educational	Honorarium for lectures

2

Learning Objectives

- To understand the risks to the offspring associated with use of valproate during pregnancy
- To be able to make risk-benefit assessments of valproate and treatment alternatives in different clinical settings
- To understand the importance of shared decision making between the prescriber and the informed patient

3

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2014
EMA/709243/2014

CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls

Women to be better informed of risks of valproate use in pregnancy and need for contraception

The CMDh,* a regulatory body representing EU Member States, has agreed to strengthen warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. The warnings aim to ensure that patients are aware of the risks and that they take valproate only when clearly necessary.

Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

4

FDA on valproate and pregnancy

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health — Drug Safety Communications

FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children

Safety Announcement

[05-06-2013] The U.S. Food and Drug Administration (FDA) is advising health care professionals and

"With regard to valproate use in pregnant women with epilepsy or bipolar disorders, valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable."

"With regard to women of childbearing age who are not pregnant, valproate should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should use effective birth control."

5

Concerns from the epilepsy community

- Treatment alternatives are few for generalized idiopathic/genetic epilepsies
  - → Efficacy of alternatives may not be comparable to VPA, and/or teratogenic risks significant, or not yet fully assessed
- Unlike men, women and girls with epilepsy risk to be denied the most effective treatment
- The risks with uncontrolled seizures may be neglected
- Women may be encourged to rapid discontinuation or switch from VPA, even during pregnancy
  - → With potentially serious consequences for them and for fetus
  - → With lack of evidence for reduction in teratogenic risks

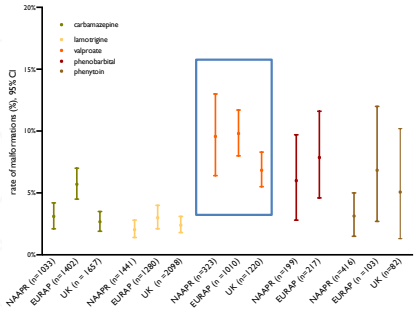
6

Risks of and with with poorly controlled seizures

- For some epilepsies VPA is the most effective treatment
  - → Generalized genetic epilepsies[1]
- Uncontrolled seizures are in general associated with serious consequences[2]
- Epilepsy associated with particularly serious risks for the pregnant woman [3,4]
  - → Epilepsy-related deaths (mainly SUDEP) accounted for 4%-7% of all maternal deaths in UK; 10-fold higher than expected
  - → More than 10-fold increased risk of death during delivery hospitalization in the US in women with epilepsy
- Uncontrolled maternal seizures may adversely affect the fetus [5-8]

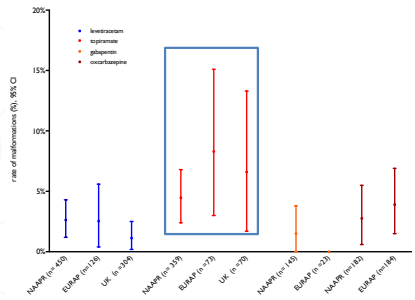
[1]Marson AG et al, Lancet 2007; [2]Tomson et al, Epilepsy Res 2004; [3]Edey et al., Epilepsia 2014 ; [4]MacDonald et al., JAMA Neurol 2015 ; [5]Adab N, et al. J Neurol Neurosurg Psychiatry 2004; [6]Cummings et al., Arch Dis Child 2011; [7]Hiilesmaa et al Am J Obstet Gynecol 1985;. [8]Teramo et al., J Perinat Med 1979

Malformation (MCM) risks higher with valproate Data from pregnancy registries



Tomson et al., Lancet Neurol 2011, Tomson et al., Neurology 2015, Hernandez-Diaz et al., Neurology 2012, Campbell et al., JNNP 2014

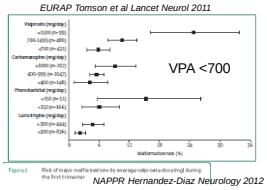
MCM risks in monotherapy More data needed on other newer AEDs



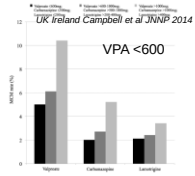
Tomson et al., Lancet Neurol 2011, Hernandez-Diaz et al., Neurology 2012, Hunt et al., Neurology 2008, Mawhinney et al., Neurology 2013,

The MCM risk depends on the dose

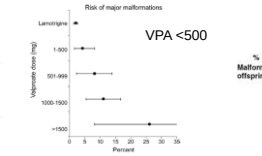
EURAP Tomson et al Lancet Neurol 2011



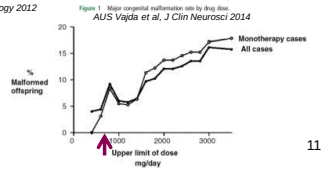
UK Ireland Campbell et al JNNP 2014



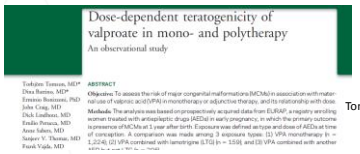
NAPPR Hernandez-Diaz Neurology 2012



AUS Vajda et al, J Clin Neurosci 2014



Adding one other AED to valproate has no major impact on MCM frequency



Dose-dependent teratogenicity of valproate in mono- and polytherapy
An observational study

Tomson et al., Neurology 2015;85:866-72

	VPA mono N=1224	VPA+LTG N=159	VPA+Other N=205	P-value
MCM Rate (95% CI)	10.0 % (8.4-11.8)	11.3% (7.3-17.2)	11.7% (8.0-16.8)	P=0.6900*
Median VPA dose, mg/day (IQ range)	800 (500)	800 (500)	1000 (900)	P<0.0001**

Valproate can affect cognitive development


The NEW ENGLAND JOURNAL of MEDICINE

Meador et al., NEJM 2009

Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Outcome at 3 years

Neurodevelopmental **E**ffects of **A**ntiepileptic **D**rugs, **NEAD** Study
309 mother/child pairs from 25 centers in US & UK

Table 2. IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.*

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

NEAD: Outcome at 6 years and dose-dependency

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Meador et al., Lancet Neurol 2013

	CBZ	LTG	PHT	VPA
Completers, n	61	74	40	49
Mean IQ (95% CI)	106 (103-109)	108 (105-111)	109 (105-113)	98 (95-102)

Dose	CBZ	LTG	PHT	VPA
Low	107	106	108	104
High	106	109	106	**94**

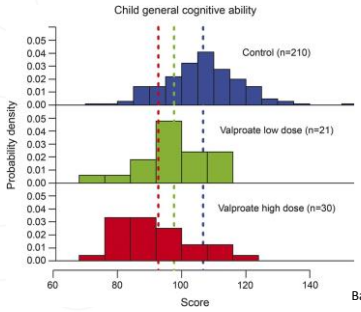
Median Dose
CBZ 800 mg
LTG 500 mg
PHT 400 mg
VPA 1000 mg

IQ at 6 years after in utero exposure to antiepileptic drugs
A controlled cohort study

Baker et al., Neurology 2015

- 173 children of women with epilepsy with AEDs (17% drop-out)
  - 143 monotherapy; 30 polytherapy
- Significant overlap with the NEAD study, 46%
- 25 children of untreated women with epilepsy
- 210 control children of healthy mothers

IQ at 6 years in VPA exposed and controls



At VPA <800 mg/d
- IQ not different
- Verbal abilities impaired
- Educational interventions increased

Baker et al., Neurology 2015

Autism and ASD after exposure to VPA

Christenssen et al JAMA 2013

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Wood et al Epilepsia 2015

Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy

Absolute risk of autism spectrum disorder 4.4% (2.6-7.5%) after VPA exposure

VPA mono	n=26
CBZ mono	n=34
LTG mono	n=9
VPA poly	n=15
Other poly	n=19

Childhood Autism Rating Scale at 6-8 years

Figure 1. CARS scores of AED-exposed children.

Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review)

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG

THE COCHRANE COLLABORATION®

Authors' conclusions

"The most important finding is the reductions in IQ in the VPA exposed group, which are sufficient to affect education and occupational outcomes in later life. …" "We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk."

Bromley et al., The Cochrane Library 2014, volume 10

SPECIAL REPORT

Task Force appointed by ILAE-CEA and European Academy of Neurology

Valproate in the treatment of epilepsy in girls and women of childbearing potential

Epilepsia 2015;56:1006-19

Wherever possible, valproate should be avoided in the treatment of girls and women of childbearing potential

…but which are the situations when valproate cannot be avoided? And when can valproate still be used within the remit of the new EMA restrictions?

The Task Force took the following into consideration

- The teratogenic risks with valproate AND with treatment alternatives
  - → Noted the pronounced risks with valproate and the dose-dependency
  - ks with
- **Over-riding principle**
  The informed patient's right to express a preference and the principle of shared decision between physician and patient
- the treatment of different epilepsies
  - → Noted the multitude of alternatives for focal epilepsies
  - → Noted the limited options for some generalized epilepsies
- Risks and benefits of different treatment alternatives in specific clinical situations

Epilepsia 2015;56:1006-19

General recommendations

1. Female patients on VPA should be informed about the teratogenic risks, and of possibilities and limitations of prenatal screening, which cannot identify children whose neurodevelopment will be affected.
2. VPA should preferably not be used for focal epilepsy. Withdrawal or switch to alternatives should be considered for women of childbearing potential established on VPA for focal seizures and who consider pregnancy.
3. If used in women of childbearing potential, VPA should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500-600 mg/day.
4. Women of childbearing potential who are not planning pregnancy and continue treatment with VPA should utilize effective birth control.

Epilepsia 2015;56:1006-19

Newly diagnosed epilepsy

- VPA and alternatives should be considered for generalized epilepsies (e.g. JME, JAE) where VPA is more effective than other drugs. VPA may be prescribed provided that
  - → The fully informed woman chooses VPA, and
  - → Is not planning pregnancy
- When most appropriate for seizure/epilepsy type, VPA may be considered for girls with epilepsies with high likelihood of remission and AED withdrawal before puberty
- When most appropriate for seizure/epilepsy type VPA may be considered when the epilepsy is so severe, or concurrent disabilites so severe, that pregnancy is extremely unlikely

Epilepsia 2015;56:1006-19

Patient established on valproate, not considering pregnancy

- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- For those with suboptimal seizure control or adverse effects on VPA, a switch should be considered
- VPA can be continued in GGE, when, after careful information, patient and clinician agree that benefits of remaining outweigh risks of withdrawal or switch
- Those whose seizures were only controlled after failing other appropriate alternatives, and for whom risks of withdrawal are not acceptable, can continue on VPA
- Women who wish to continue on VPA, but are willing to accept risks with dose reduction, aim for doses not exceeding 500-600 mg/day

Epilepsia 2015;56:1006-19

Patient established on valproate considering future pregnancy

- Treatment should be reassessed and changes carefully considered for every women considering pregnancy
- Switch or withdrawal should always be considered in focal epilepsy
- Treatment changes shuld be completed and evaluated before conception. Lowest effective dose established before conception
- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- Switch from VPA to alternative should be considered for those not suitable for, or who have failed, treatment withdrawal
- Continued VPA can be considered for those well controlled on low dose VPA (up to 500-600 mg/day), AND who consider risk of withdrawal or switch unacceptable

Epilepsia 2015;56:1006-19

Women already on valproate while pregnant

- The general rule is to continue treatment with VPA in patients discovering that they are pregnant
- Withdrawal of VPA in a pregnant woman should only be initiated if the risk of doing so is acceptable to the patient.
  - Usually the case only when there is agreement that treatment is not needed for acceptabe seizure control
- Reduction in VPA dose can be considered when the risk of doing so is acceptable to the patient.
  - Usually only the case when prior history suggests that dose is higher than needed for acceptable seizure control
- Switch to other treatment generally not recommended during pregnancy in patient with good seizure control

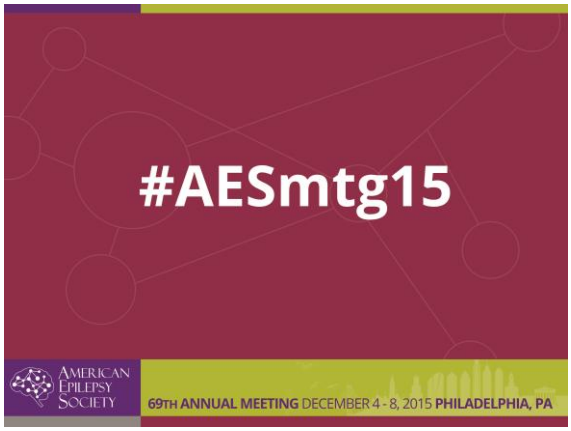
Epilepsia 2015;56:1006-19

Impact on Clinical Care and Practice

- Whenever possible valproate should be avoided in women of childbearing potential
  - Teratogenic risks need to be considered at time of initiation of treatment
  - Treatment needs to be reassessed regularly and always before conception
- Teratogenic risks need to be weighed against efficacy
  - Risks and benefits of reasonable treatment alternatives need to be assessed and discussed
  - The choice of treatment is a shared decision between clinician and patient

26

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING



Cannabis Update

Kelly Knupp, MD
Associate Professor of Pediatrics and Neurology
University of Colorado, Anschutz Medical Campus
Aurora, CO

December 8, 2015

Disclosure

AES infrastructure grant	Zongenix
Colorado Department of Public Health and environment	Turing pharmaceuticals

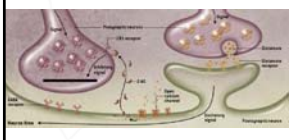
Learning Objectives

Review common terms and the endocannabinoid system
Discuss preclinical studies
Discuss recent human data

Neurobiology: Endocannabinoid System

- Most abundant G-protein coupled receptor in the brain
  - CB1R – **hippocampus**, association cortices, **basal ganglia**, **cerebellum**, DRG, peripheral nerves
  - CB2R – lymph tissue, pancreas, intestine, retina, low concentrations in CNS

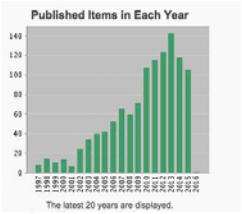
Endocannabinoids



- Rapid synthesis, activation, and degradation suggest that compounds are neuromodulators
- Dose and activity dependent
- Additional therapeutic targets include inactivation inhibitors which could increase neurotransmission only in active synapses minimizing side effects

- Synthesized on demand by neurons after depolarization and increased intracellular Ca^{++}
- Travel retrograde to cleft and bind to CB1 receptors in the pre-synaptic neuron
- Activation leads to:
  - Opening K^{+}channels
  - Closure of Ca^{++}channels
  - Inhibition of adenylyl cyclase
  - Stimulation of kinases
  - Inhibit neurotransmitter release

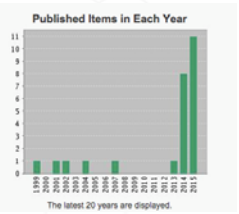
Cannabidiol



Field: Document Types	Record Count	% of 1432	Bar Chart
ARTICLE	1031	71.997 %	
MEETING ABSTRACT	182	12.709 %	
REVIEW	150	10.475 %	
PROCEEDINGS PAPER	41	2.863 %	
EDITORIAL MATERIAL	24	1.676 %	
NOTE	22	1.536 %	
LETTER	15	1.047 %	
CORRECTION	7	0.489 %	
BOOK CHAPTER	4	0.279 %	

Webofknowledge.com

Medical Marijuana and Epilepsy



Field: Document Types	Record Count	% of 25	Bar Chart
ARTICLE	11	44.000 %	
REVIEW	9	36.000 %	
EDITORIAL MATERIAL	5	20.000 %	

Webofknowledge.com

What have we learned

Not <u>all</u> cannabinoids act via the endocannabinoid system

- Of ~100 plant cannabinoids, only 3 are CB1R/CB2R ligands:
  - **Δ^9-THC (tetrahydrocannabinol)**
    - Principal psychoactive component
    - Partial agonist at CB1R and CB2R
  - **CBN (cannabinol)**
    - Agonist
    - ~50x times less potent than Δ^9-THC
  - **THCV (tetrahydrocannabivarin)**
    - Neutral antagonist at CB1R and a partial agonist at CB2R

Summary Of Preclinical Evidence

- Large preclinical evidence base asserting mixed effects on seizures in animal models

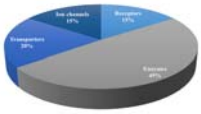
Compound	Species	Number of discrete conditions/models/designs	Dose	Anticonvulsant	No effect	Proconvulsant
THC	6	31	0.25-200 mg/kg	61%	29%	10%*
CBD	2	21	1-400 mg/kg	81%	19%	0%
Other plant cannabinoids	2	7	N/A	100%	0%	0%
CB1 receptor agonists	2	55	N/A	73%	18%	2% (7% mixed effect
CB1 receptor antagonists	2	9	N/A	9%**	61%**	30%**

*Includes non-seizure studies where convulsions were reported.
**% values rounded up.

Whalley (2014) Cannabis and Seizures American Herbal Pharmacopeia

Mechanisms Underlying CBD Anti-epileptic Effects

- CBD has 65 discrete molecular targets documented in published literature (PMID: 26264914)
- Many effects only manifest at high µM or mM concentrations making them implausible mediators of CBD's anti-epileptic effects (PMID: 21796370)
- All are *in vitro* and have not been definitively linked to functional effects in whole animals/humans
- Some effects appear to be tissue and excitability dependent
- Targets can be limited by considering:
  - Effects at physiologically achievable concentrations
  - Known involvement of targets in disease states
  - Direction of effect consistent with beneficial effects



Disease or disease group	Most plausible molecular targets of CBD
Epilepsy	TRPV1 (desensitised), VDAC1, CaV3.x, 5HT1A, GlyR, GPR55, adenosine modulation (ENT1)

Cocaine Induced Seizures

- URB597 inhibits FAAH (enzyme that breaks down anadamide)
- URB597 protects against cocaine induced seizures
  - Increased time to seizure and reduced seizure duration
- Also was protective against cFos expression and cell death in the hippoocampus from cocaine

Vilela L et al, Tox and applied pharmacology, 2015

Kainic Acid Induced Seizures

- First demonstrated that there are changes with age in the hippocampal regions: CB1R, CB2R and FAAH
- After KA induced seizures, endocannabinoid differences were found by age
  - AEA increased in young animals, lowered in older animals
  - 2AG decreased in young animals, increased in older
- Enhancing respective eCB lead to protection from seizures

Fezza F et al, Molecular And Cellular Neuroscience, 2014

HUMAN STUDIES

Survey Results

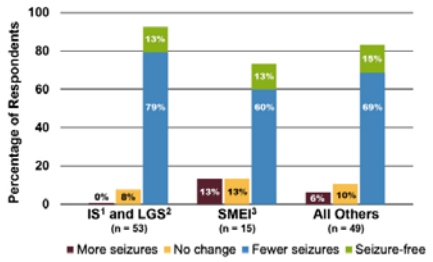


Fig. 1. Perceived response to CBD exposure. [1]Infantile spasms. [2]Lennox–Gastaut syndrome. [3]Severe myoclonic epilepsy of infancy (Dravet syndrome).

Hussain S, Epilepsy & Behavior 2015

Clinical Evidence: Retrospective study

- N = 75 (average age 7y)
  - 1/3 report a 50% reduction in seizures
  - Response rate similar with all products
  - Families that moved from out of state 2x more likely to report an improvement
  - Response rate varied by syndrome LGS>Dravet
  - 11 patients (15%) discontinued treatment, largely due to inefficacy
  - 2 patients seizure free

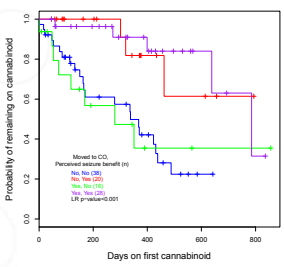
Press, C Epilepsy & Behavior 2015

Clinical Evidence: Retrospective Study

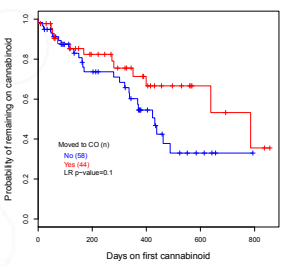
- Adverse events in 44%
  - Increased or new seizures in 13%
  - Fatigue 12%
  - GI symptoms 11%
  - Rare events: developmental regression, new movement disorder, transient hemiparesis, cholecystitis, opisthotonus, status epilepticus requiring intubation, and death
- Benefits outside seizure reduction
  - Improved behavior/alertness in 25 (33%)
  - Improved language (i.e., now using three words) in 8 (11%)
  - Improved motor skills in 8 (11%)

Press, C Epilepsy & Behavior 2015

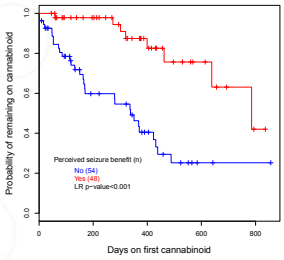
Time to Cessation



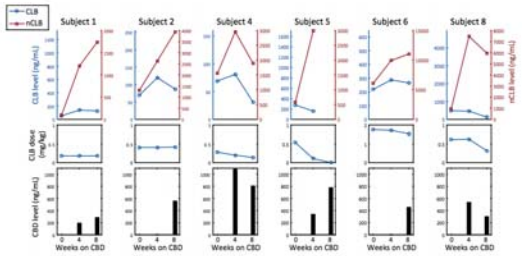
Time To Cessation: Resident Vs Nonresident



Perceived Seizure Benefit And Cessation



CBD Affects Clobazam Levels



Geffrey A et al, Epilepsia 2015

CBD/ clobazam interaction

- N=13
- Increased clobazam levels mean 60% (CI -2-91%)
- nCLB levels mean increase 500% (CI 90-610)
- 10 of 13 subjects decreased clobazam based on side effects

EA Safety Data (Epidiolex)

- 261 pts (3 months treatment)
- Response rate (median seizure reduction)
  - overall 45.1%
  - Dravet syndrome 62.7%
  - LGS – 71.1% (tonic seizure)
- Seizure freedom in 9%
- Common adverse events
  - Somnolence - 23%
  - Diarrhea - 23%
  - Fatigue - 17%
  - Decreased appetite - 17%
  - Convulsions – 17%
  - Vomiting – 10%
- No changes in hematologic or renal markers
- SAE in 106 patients, 7 deaths
  - 16 treatment related: altered liver enzymes(4) status epilepticus(4), diarrhea (4), weight loss (3), thrombocytopenia (1)

Devinski O et al, AES abstract 2015

Epilepsy: Upcoming Research

- Epidiolex Study
  - A Double-blind, Placebo-controlled, Phase III trial Efficacy and Safety Of Cannabidiol (GWP42003-P) In Children And Young Adults With Dravet Syndrome and Lennox-Gastaut Syndrome
  - Epidiolex – 98-99% CBD
  - 3 dose levels, 2 week titration, 12 week maintanence period
  - Approximately 150 patients, multicenter, enrollment 9/14–1/15
- Additional studies
  - Phase III studies for Tuberous Sclerosis
  - CBDV – Phase I in healthy adults followed by Phase II in patients with epilepsy
  - Synthetic CBD for epilepsy

Conclusion

- Over the last 30 years there has been research on the endocannabinoid system
  - It is complex
  - There is more to understand
  - May be a good target for new pharmaceuticals
- CBD appears to alter metabolism of other medications
- Clinical studies of pharmaceutical products are occurring now
- There is lot more work to be done!