Overview
Infantile spasms, also known as West syndrome, is a catastrophic childhood epilepsy with seizures that are difficult to control; it is associated with mental retardation. It usually has an onset during the first year of life, and typically between 4 and 8 months. Early recognition, careful diagnostic evaluation, and proper treatment may allow some children to attain seizure control and achieve a normal or much improved level of development, with complete control of spasms as the goal. This symposium will present the latest evidence-based studies related to the diagnosis and management of infantile spasms.

Learning Objectives
- Assess the need for early diagnostic evaluation and etiologic diagnosis of infantile spasms for optimization of long-term developmental outcomes of patients
- Explain the rationale for developing a treatment plan that has a goal of complete control of infantile spasms
- Compare the efficacy, adverse effects, and difficulties of treating infantile spasms with adrenocorticotropic hormone (ACTH) or vigabatrin
- Contrast the efficacy of ACTH and vigabatrin with other available therapies, including non-drug options

Intended Audience
This program is intended for the education of pediatric neurologists and other health care providers involved in the management and treatment of patients with infantile spasms.

Program Agenda
7:00 PM Dinner and Introductions
7:30 PM Overview: Treatment and Developmental Outcomes
   Dr. W. Donald Shields
7:45 PM Timing and Efficacy of Therapy: Is Sooner Really Better?
   Dr. Elizabeth Thiele
8:05 PM Case Study #1—ACTH, the Gold Standard: Efficacy and Side Effects
   Dr. Shlomo Shinnar
8:25 PM Case Study #2—Vigabatrin: What Is Its Role in Treating Infantile Spasms?
   Dr. John M. Pellock
8:45 PM Efficacies of Other Available Therapies
   Dr. Tracy A. Glauser
9:05 PM Panel Discussion and Q&A
9:30 PM Adjournment

ACCREDITATION AND DESIGNATION
The Chatham Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Chatham Institute designates this educational activity for a maximum of 2.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Sponsored by
The Chatham Institute

Supported by educational grants from
Lundbeck

QUESTCOR
Faculty

W. Donald Shields, MD — Program Chair
Division of Pediatric Neurology
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, CA

W. Donald Shields, MD is professor of neurology and pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.

Dr. Shields received his medical degree from the University of Utah College of Medicine. He completed his internship and residency in pediatric medicine at the Los Angeles County-University of Southern California Medical Center. He also completed a residency in neurology and a fellowship in pediatric neurology at the University of Utah College of Medicine.

Dr. Shields has been a member of the Child Neurology Society, Professors of Child Neurology, American Academy of Neurology, American Academy of Pediatrics, and American Epilepsy Society. He has been investigator or co-investigator on 30 funded grants. Dr. Shields has authored or co-authored over 100 articles and over 30 book chapters, and has written or co-written over 80 abstracts and 2 book reviews.

Tracy A. Glauser, MD
Director, Comprehensive Epilepsy Center
Cincinnati Children’s Hospital Medical Center
Cincinnati, OH

Tracy A. Glauser, MD is a professor of pediatrics, the director of the Comprehensive Epilepsy Center, and the Co-Director of the Genetic Pharmacology Service at Cincinnati Children’s Hospital Medical Center in Cincinnati.

Dr. Glauser received his medical degree, cum laude, from Jefferson Medical College in Philadelphia. He completed his residency in pediatrics at The Johns Hopkins Hospital in Baltimore, and a fellowship in child neurology at The Children’s Hospital of Philadelphia, University of Pennsylvania. Dr. Glauser completed a National Institute of Neurological Disorders and Stroke research fellowship in pediatric neurology and was a fellow in epilepsy and electroencephalography at St. Louis Children’s Hospital, Washington University School of Medicine in St. Louis.

Dr. Glauser has authored or co-authored more than 130 articles and book chapters, has been involved with the development of 6 evidence-based guidelines about epilepsy therapy, and has given over 150 invited lectures throughout the world. He has been the principal investigator on multiple NIH grants. Currently, Dr. Glauser directs the NIH-funded Childhood Absence Epilepsy clinical trial involving 32 pediatric centers around the United States. Dr. Glauser’s fields of expertise are pediatric neurology, pediatric epilepsy, clinical pharmacology, and pharmacogenetics.
Treatment Approaches in
Infantile Spasms

Faculty (continued)

John M. Pellock, MD
Chairman, Division of Child Neurology
Vice Chairman, Department of Neurology
Virginia Commonwealth University Health System
Richmond, VA

John M. (Jack) Pellock, MD is chairman of the Division of Child Neurology, vice chairman of the Department of Neurology, and professor of neurology, pediatrics, pharmacy, and pharmaceutics at the Medical College of Virginia, Virginia Commonwealth University Health System, in Richmond.

Dr. Pellock received his undergraduate degree from Johns Hopkins University, a master of science in biology at Fairleigh Dickinson University in Teaneck, New Jersey, and his medical degree from St. Louis University in St. Louis, Missouri. He completed an internship and residency in pediatrics at the Medical College of Virginia, and a fellowship in pediatric neurology at Columbia Presbyterian Medical Center in New York.

Dr. Pellock is a diplomate of the American Board of Pediatrics and of the American Board of Psychiatry and Neurology with Special Qualification in Child Neurology. He is a fellow of the American Academy of Neurology and the American Academy of Pediatrics, and is a member of several other professional organizations, including the American Neurological Association, the Child Neurology Society, and the American Epilepsy Society, where he has served as treasurer and is currently 2nd vice president (president elect, 2011). He has been included in Best Doctors in America and Who’s Who International and America. Dr. Pellock has been principal investigator for over 90 trials evaluating epilepsy treatments in children and adults, and a co-investigator for many others. He is funded by the NIH for various studies in pediatric and adult epilepsy. Dr. Pellock has been involved in antiepileptic drug development and studying epilepsy in children for over 30 years. He is a member of the Editorial Boards of the Journal of Child Neurology, Pediatric Neurology, Epileptic Disorders, and Journal of Pediatric Pharmacology and Therapeutics, and serves as reviewer for a number of journals, including the New England Journal of Medicine, Neurology, Epilepsia, and Pediatrics. He has published extensively and lectured widely on pediatric epilepsy and has conducted clinical research in anticonvulsant therapy. He received the 2004 J. Kiffin Penny Award for Excellence in Neurology from the American Epilepsy Society.

Shlomo Shinnar, MD, PhD
Professor of Neurology and Pediatrics
Hyman Climenko Professor of Neuroscience Research
Director, Comprehensive Epilepsy Management Center
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, NY

Shlomo Shinnar, MD, PhD is professor of neurology, pediatrics, and epidemiology and population health, the Hyman Climenko Professor of Neuroscience Research, and director of the Comprehensive Epilepsy Management Center at Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

Dr. Shinnar received a bachelor of arts degree, summa cum laude, in physics from Columbia College in New York. He was a predoctoral fellow with the NIH Medical Scientist Training Program at Albert Einstein College of Medicine, where he received a doctor of philosophy degree in neurophysiology and a doctor of medicine degree. He then trained in pediatrics and child neurology at The Johns Hopkins Hospital in Baltimore. He has been at Montefiore Medical Center and the Albert Einstein College of Medicine since 1983.

Dr. Shinnar is board certified by the American Board of Psychiatry and Neurology (in neurology, with special competence in child neurology and added qualification in clinical neurophysiology) and the American Board of Pediatrics. He is a fellow of the American Academy of Neurology and the American Academy of Pediatrics, and a member of the American Neurological Association and the
Faculty (continued)

Society for Pediatric Research. He has been active in the American Epilepsy Society and the Epilepsy Foundation of America. He has also been active in local epilepsy societies, including the Epilepsy Foundation of Southern New York and the Epilepsy Institute.

Dr. Shinnar is well known for his research on a variety of topics relating to childhood seizures and language regression, including when to initiate and discontinue antiepileptic drug therapy, prognosis following a first seizure, prognosis following discontinuation of medications in children with seizures, status epilepticus, febrile seizures, and language regression and its relationship to autism and seizures. His major contributions have focused on epidemiological investigations of long-term outcomes of childhood seizures. Dr. Shinnar has been the principal investigator or co-investigator on a variety of NIH-funded research studies. He is the principal investigator of a large multicenter study, “Consequences of Prolonged Febrile Seizures in Childhood.” He is also a member of the executive committee and co-investigator of a large multicenter NIH-funded study, “Childhood Absence Epilepsy: Rx, PK-PD Pharmacogenetics.” He has also been involved in industry-sponsored trials of new medications. Dr. Shinnar is a recipient of the Research Recognition Award of the American Epilepsy Society. He has authored over 150 papers and is the senior editor of the book Childhood Seizures and coeditor of the recently published Febrile Seizures. His current research efforts combine careful epidemiological approaches with modern imaging, neurophysiological, and neuropsychological studies to examine the causes and long-term consequences of childhood seizures.

Elizabeth Thiele, MD, PhD
Director, Pediatric Epilepsy Program
Director, Tuberous Sclerosis Comprehensive Clinical Program
Massachusetts General Hospital
Boston, MA

Elizabeth A. Thiele, MD, PhD is director of the Pediatric Epilepsy Program and director of the Carol and James Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital. She is also associate professor of neurology at Harvard Medical School.

Dr. Thiele received her AB summa cum laude from Washington University in St. Louis and her MD and PhD from the Johns Hopkins University School of Medicine. She completed a residency in pediatrics at The Johns Hopkins Hospital in Baltimore and a residency in child neurology with the Longwood Program and Children’s Hospital in Boston. In addition, she completed a neuroscience fellowship at Children’s Hospital in Boston. Dr. Thiele is board certified in neurology with a special qualification in child neurology and in clinical neurophysiology.

Dr. Thiele serves on the Board of Directors of the Tuberous Sclerosis Alliance, and is also a member of the American Epilepsy Society, the Child Neurology Society, and the Greater Boston Epilepsy Society, and is on the Scientific Advisory Board of the Angelman Syndrome Foundation. Dr. Thiele directs clinical research efforts in the neurologic aspects of tuberous sclerosis complex, including epilepsy, autism, and mental health issues, as well as work on improved dietary therapies for epilepsy, including low glycemic index treatment. Dr. Thiele has received awards for teaching in residency programs at Massachusetts General Hospital and the Longwood Neurology Program, and for research mentoring from the Harvard-MIT Health Sciences and Technology program, and was nominated for a Humanism in Medicine Award from Harvard Medical School.
Facility Disclosures

It is the policy of The Chatham Institute to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. All faculty, planners, and managers who affect the content of medical education activities sponsored by The Chatham Institute are required to disclose to the audience any real or apparent conflict of interest related to the activity. Faculty, planners, and managers not complying with the disclosure policy will not be permitted to participate in this activity.

Program faculty and planners have disclosed the financial relationships with commercial interests cited below. All program content has been peer reviewed for balance and any potential bias. The conflict of interest resolution process aims to ensure that financial relationships with commercial interests and resultant loyalties do not supersede the public interest in the design and delivery of continuing medical education activities for the profession.

All speakers and planners have agreed that this activity will be free of bias.

W. Donald Shields, MD
Grants: Ovation Pharmaceuticals, Questcor
Consultant: Ovation/Lundbeck, Questcor

Tracy A. Glauser, MD
Advisory Boards: Johnson & Johnson, UCB Pharma, Inc.
Consultant: Johnson & Johnson, UCB Pharma, Inc.
Speaker Bureaus: UCB Pharma, Inc.
Stock Shareholder: Questcor Pharmaceuticals
Received Study Medicine for NIH-funded Trial: Abbott Laboratories, GlaxoSmithKline, Lundbeck Pharmaceuticals
Clinical Trial Data and Safety Monitoring Board: Lundbeck Pharmaceuticals

John M. Pellock, MD
Lecturer: Abbott Laboratories, Cephalon, Inc., Eisia, Inc., GlaxoSmithKline, MedPointe, Novartis Pharmaceuticals Corporation, Ortho McNeil/Johnson & Johnson, Ovation Pharmaceuticals, Pfizer Inc, Questcor Pharmaceuticals, Schwarz Pharma, UCB Pharma, Inc., Valeant Pharmaceuticals

Shlomo Shinnar, MD, PhD
Advisory Boards: Questcor Pharmaceuticals
Consultant: Eisia, Inc., Johnson & Johnson, Questcor Pharmaceuticals, Valeant Pharmaceuticals
Data and Safety Monitoring Board Member: King Pharmaceuticals
Speaker Bureaus: Eisia, Inc., Questcor Pharmaceuticals, UCB Pharma, Inc., Valeant Pharmaceuticals
Research: Questcor Pharmaceuticals

Elizabeth Thiele, MD, PhD
Advisory Boards: Johnson & Johnson, UCB Pharma, Inc.
Consultant: Johnson & Johnson, UCB Pharma, Inc.
Speaker Bureaus: UCB Pharma, Inc.
Stock Shareholder: Questcor Pharmaceuticals
Received Study Medicine for NIH-funded Trial: Abbott Laboratories, GlaxoSmithKline, Lundbeck Pharmaceuticals
Clinical Trial Data and Safety Monitoring Board: Lundbeck Pharmaceuticals

THE CHATHAM INSTITUTE FINANCIAL DISCLOSURES
Daniel Duch, PhD, medical director, and Cynthia Fontán, MPA, education manager, have no real or apparent relationships to disclose.
An Exciting Time for Treatment of Infantile Spasms Patients

List of all drugs approved by the FDA for the treatment of infantile spasms
IS Symposium

What Are the Issues?
- Delay in diagnosis of IS
  - Pediatricians vs peds neurologists
- Delay in initiation of effective treatment
  - Peds neurologists
- How is “effective” defined?

DDx Infantile Spasms

CRYPTOGENIC

- Cerebral Dysplasia
- Focal Cortical Dysplasia
- Hemimegalencephaly
- Bifrontal Callosal Agenesis
- Dysgenesis Syringomyelia Dysraphia
- Schizencephaly
- Multiple Pial Cysts
- Basal Insufficiency
- Acromegaly Syndrome
- Lisencephaly
- Dysembryoplastic Encephalopathy

- Pyridoxine Dependent Seizures
- Phenylketonuria
- Maple Syrup Urine Disease
- Medium Chain Triglyceride Deficiency
- Menkes Disease
- Hypophosphatemic Osteodystrophy
- Non-ketotic Hyperglycinemia
- Leigh Disease
- Kallmann Disease
- ARA

Infantile Spasms: Definition of Responder

- In the American Academy of Neurology (AAN) and Child Neurology Society (CNS) practice parameter, a responder is characterized by
  - Complete cessation of spasms, as confirmed by video electroencephalogram (EEG)
  - Abolition of hypsarrhythmia on prolonged EEG

Infantile Spasms: Definition of Responder

- The AAN/CNS practice parameter definition of response as an “all or none” phenomenon is very different from the usual definition of 50% reduction in seizures
- It reflects our understanding of the pathophysiology of the disease
  - Unless one abolishes the hypsarrhythmia, there is progression and cognitive decline

Infantile Spasms: Definition of Responder

- Why is abolition of hypsarrhythmia important?
  - It doesn’t matter if you eliminate focal spikes in CPS. Why is it important in IS?
- MY VIEW
  - Spasms are the clinical manifestation of an underlying encephalopathy
  - Hypsarrhythmia is the EEG manifestation of an underlying encephalopathy
- THE GOAL OF THERAPY IS TO TREAT THE ENCEPHALOPATHY, Not the Seizures!

Infantile Spasms

**ACTH: The Gold Standard**
- (But Not FDA Approved)
  - Requires Specialty Pharmacy
  - Side effects

**Vigabatrin: The only FDA-approved Rx**
- Requires Specialty Pharmacy
- REMS
- Side effects

Is the pain worth the gain?
Infantile Spasm Treatment Guidelines

<table>
<thead>
<tr>
<th>Infantile Spasms</th>
<th>AAN Practice Parameter</th>
<th>SIGN Epilepsies in Children and Young People</th>
<th>Nice (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids probably effective</td>
<td>VGB possibly effective for IS and IS with TS</td>
<td>Steroids first line, VGB “superior” when IS secondary to TS</td>
<td>VGB and steroids first-line therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infantile Spasms Secondary to TS</th>
<th>European Expert Opinion</th>
<th>US Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGB Rx of choice</td>
<td>VGB Rx of choice</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infantile Spasms – Symptomatic</th>
<th>European Expert Opinion</th>
<th>US Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGB Rx of choice, ACTH, prednisone also first line</td>
<td>ACTH, topiramate Rx of choice, VGB sometimes appropriate</td>
<td></td>
</tr>
</tbody>
</table>

IS Symposium Program

Elizabeth Thiele
- Does Treatment Matter?
- Does Timing of Treatment Affect Outcome?

Shlomo Shinnar
- Hormonal Therapy
  - ACTH and Oral Steroids

Jack Pellock
- Vigabatrin

Tracy Glauser
- Other Therapies
  - Valproate, Ketogenic Diet, Topiramate, Zonisamide, etc, etc

Q & A

Timing and Efficacy of Therapy: Is Sooner Really Better?

Elizabeth A. Thiele, MD, PhD
Director, Pediatric Epilepsy Program
Director, Herscot Center for TSC
Massachusetts General Hospital
Harvard Medical School
Infantile Spasms: What Affects Outcome?

- Etiology?
  - Symptomatic?
  - Idiopathic?
- EEG pattern at diagnosis? EEG “response” to treatment?
- Presence of other seizure types?
  - Before, after, or during infantile spasms (IS)?
- Developmental regression or plateauing with onset of spasms?
- Presence of other neurologic signs/symptoms?

Infantile Spasms: What Affects Outcome?

- Efficacy of treatment?
- Age at IS onset?
- Timing?
  - Time from onset of IS to diagnosis and treatment?
  - Time from onset to complete IS control?

Timing and Efficacy of Therapy: Is Sooner Really Better?

... YES!!!!!

- IS in tuberous sclerosis complex (TSC):
  - Clinical variables
  - EEG characteristics
  - Role of vigabatrin
- And is there other evidence?
Tuberous Sclerosis Complex
- Autosomal dominant disorder affecting 1:5500
- Multisystem involvement
- TSC1 and TSC2 genes
  - TSC2 mutations 6x more common than TSC1
  - TSC2 mutation more severe phenotype
- Cognitive impairment in 50%, autism spectrum disorders in 40%

Epilepsy most common symptom, affecting 95% of individuals; 70% with seizure onset <1 year of age
- Infantile spasms occur in one-third
  - But, one-third of children with TSC and IS have subsequent normal cognitive outcome
- “Model” system for studying IS

Retrospective study of 50 infants with TSC and IS
- Age at spasm onset: 6.8 mo (range, 1 d to 24 mo)
- Time from IS onset to treatment initiation: 3.5 mo (range, 0 to >24 mo)
- Time from treatment initiation to IS cessation: 11.1 mo (range, 0 to >24 mo)
- Time from IS onset to IS cessation: 13.0 mo (range, 0 to >24 mo)

IS and TSC: What Factors Affect Outcome?

MGH Herscot Center for TSC Experience

- Retrospective study of 50 TSC patients with history of IS
  - IS clinical characteristics, including timing at 1-mo intervals
  - Intellectual status (IQ or DQ) <70 or >70
  - Ongoing seizures after IS cessation
    - Well controlled vs poorly controlled (>2 seizures per month)
  - 80 TSC patients without IS “control”


MGH Herscot Center for TSC Experience

- Of those with TSC and IS:
  - Age at spasm onset: 6.8 mo (range, 1 d to 24 mo)
  - Time from IS onset to treatment initiation: 3.5 mo (range, 0 to >24 mo)
  - Time from treatment initiation to IS cessation: 11.1 mo (range, 0 to >24 mo)
  - Time from IS onset to IS cessation: 13.0 mo (range, 0 to >24 mo)


IS and TSC: What Factors Affect Outcome?

MGH Herscot Center for TSC Experience

- 32/50 (64%) with subsequent mental retardation (MR) (IQ/DQ <70)
  - But, one-third with normal cognitive outcome
- 3 variables associated with MR:
  - Increased duration of IS from onset to cessation
  - Risk of MR increased with each month of uncontrolled IS
  - Increased time from treatment initiation to IS cessation
  - Poor control of other seizures after IS

IS and TSC: What Factors Affect Outcome?

MGH Herscot Center for TSC Experience

- Retrospective study of 45 TSC patients with h/o IS and with available EEG from time of diagnosis
  - Age at IS onset, 7.1 ± 5.1 mo (range, 1.0-29.0 mo)
  - Age at IS cessation, 15.3 ± 12.0 mo (range, 3.0-60.0 mo)
  - 76% with subsequent MR (IQ <70)

IS and TSC: What Factors Affect Outcome?

MGH Herscot Center for TSC Experience

- Lower IQ associated with EEG features of:
  - Higher hypsarrhythmia scores on EEG report
  - Presence of background disorganization
  - Absence of normal sleep patterns
- Lower IQ also associated with lack of success of vigabatrin
  - Not seen for patients treated with ACTH, although dosing not known

IS and TSC: What Factors Affect Outcome?

MGH Herscot Center for TSC Experience

- Lower IQ also associated with:
  - Worse epilepsy outcome
  - Development of subsequent refractory epilepsy
- Association between history of refractory epilepsy and older age of IS cessation approached significance
- Risk of unfavorable outcome of IS with regard to both cognition and epilepsy increases as IS endure
**IS and Vigabatrin: Safety and Efficacy**

**MGH Herscot Center for TSC Experience**
- 84 children treated with vigabatrin
  - 68 treated for IS
  - 59 treated for partial-onset seizures
- Vigabatrin efficacy:
  - IS controlled in 73% of infants with TSC
  - IS controlled in 27% with IS from other etiologies
  - Overall, IS controlled in 56%
- Better cognitive outcomes associated with shorter time from IS onset to vigabatrin treatment

**Timing and Efficacy of Therapy: Is Sooner Really Better? Other Evidence**

**Riikonen Review of IS Treatment and Outcome**
- Favorable prognostic factors with IS:
  - Cryptogenic etiology
  - Age of IS onset ≥4 mo
  - Absence of atypical spasms and partial seizures
  - Absence of asymmetrical EEG abnormalities
  - Short treatment lag
  - Early and sustained response to treatment

**Early Treatment of IS in TSC**
- Early treatment of IS with vigabatrin in 10 infants with TSC
- 50% seizure free at follow-up
- 30% with normal or borderline intelligence
- No patients with severe MR or autism
- “Early control of seizures has crucial role… in reducing cognitive/behavioral consequences of seizures.”
Timing and Efficacy of Therapy: Is Sooner Really Better? Other Evidence

What Differs Between Normal and Delayed Cognitive Outcomes?
- Retrospective study of 32 IS patients
  - Treatment lag, EEG findings, and seizure evolution compared between normal outcome group (12/32) and delayed-outcome group (20/32)
  - Outcomes determined at average age of 8.6 ± 4.7 years
- Results:
  - Time from IS onset to treatment longer in delayed group
  - Increased paroxysmal discharges frontally in delayed group
  - Other seizure types more common in delayed group


Timing and Efficacy of Therapy: Is Sooner Really Better? Other Evidence

Long-term Outcomes With ACTH Treatment
- 37 patients with cryptogenic IS
  - All treated with high-dose ACTH followed by taper and oral prednisone
  - Developmental assessment before and at 6-21 years of age
  - Seizure outcomes followed prospectively


Timing and Efficacy of Therapy: Is Sooner Really Better? Other Evidence

Long-term Outcomes With ACTH Treatment
- Results:
  - 22/37 treated within 1 mo of onset; 15/37 after 1-6.5 mo
  - Cognitive outcomes:
    - Normal in all (100%) of early treatment group, and in 40% of late treatment group
    - Normal in all 25 patients who had no or only mild developmental regression at presentation
    - Normal in 3/12 who had marked or severe regression before treatment
    - Early treatment associated with favorable outcome
    - Developmental regression of >1 month associated with poorer prognosis

Timing and Efficacy of Therapy: Is Sooner Really Better? Other Evidence

Analysis of Factors That Influence Outcome
- Retrospective study of 57 cases of IS
  - 17 cryptogenic, 40 symptomatic
- Variables affecting outcome:
  - Coexistence of other seizure types
  - Presence of neurologic deficit
  - Time lag in initiation of treatment
  - Affected cognitive outcome only, not seizure outcome
  - Poor response to ACTH
  - Persistent EEG abnormalities


Timing and Efficacy of Therapy: Is Sooner Really Better?

Conclusions
- Timing and efficacy of therapy clearly do matter
- However, not the only variables
- And, importantly, what does cause the cognitive impairments?
  - Spasms themselves?
  - Hypsarrhythmia, and what does that mean?
  - Relative developmental regression with onset of IS?
  - And what is that? Epileptic encephalopathy?

Conclusions (continued)
- And, importantly, because timing of cessation of spasms does seem to be an important variable, … timing from onset to diagnosis is also crucial!
Treatment of Infantile Spasms
ACTH/Oral Steroids: Efficacy and Side Effects

Shlomo Shinnar, MD, PhD
Professor of Neurology, Pediatrics, and Epidemiology and Population Health
Hyman Climenko Professor of Neuroscience Research
Director, Comprehensive Epilepsy Management Center
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York

ACTH

- 1958: ACTH administered to 7 patients; 4 responded1
- AAN/CNS practice parameter (2004)2
  - ACTH is probably effective for the short-term treatment of infantile spasms
- Review of 14 studies of ACTH therapy
  - 5 randomized controlled
  - 4 prospective open-label
  - 5 retrospective case series


ACTH: High Dose vs Prednisone (1996)

Objective
- To compare the efficacy of ACTH vs prednisone for the treatment of infantile spasms and hypersrrhythmia

Study Design
- Prospective, randomized, single-blind study
- Treated for 2 weeks
  - ACTH dosage: 150 U/m² per day, divided BID, intramuscularly
  - Prednisone dosage: 2 mg/kg per day, divided BID, orally
- Responders: resolution of spasms and hypsarrhythmia
- Patients who did not respond after 2 weeks were allowed to cross over to the alternative treatment

ACTH: High-dose ACTH vs Prednisone (1996)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response</th>
<th>Percentage of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology (n=29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>76 (22)</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>24 (7)</td>
<td></td>
</tr>
<tr>
<td>ACTH responders (n=15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH responders (n=14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone → ACTH (n=9)</td>
<td>87 (13)</td>
<td></td>
</tr>
<tr>
<td>ACTH → Prednisone (n=2)</td>
<td>50 (1)</td>
<td></td>
</tr>
<tr>
<td>Cross-over responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone → ACTH (n=9)</td>
<td>87 (13)</td>
<td></td>
</tr>
<tr>
<td>ACTH → Prednisone (n=2)</td>
<td>50 (1)</td>
<td></td>
</tr>
</tbody>
</table>

ACTH: High Dose vs Low Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Regimen</th>
<th>Response</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (high dose)</td>
<td>26 (12 symptomatic, 4 cryptogenic)</td>
<td>150 U/m2 daily for 3 wk, 80 U/m2 daily for 2 wk, 80 U/m2 QID for 3 wk, 50 U/m2 QID for 1 wk, taper over 3 wk</td>
<td>No spasms and no hypsarrhythmia in 13 of 26 patients (50%)</td>
<td>15%</td>
</tr>
<tr>
<td>ACTH (low dose)</td>
<td>24 (19 symptomatic, 5 cryptogenic)</td>
<td>20 U/d for 1 wk; if + response, then taper over 1 wk; if no + response, increase to 30 U/d for 4 wk, then taper over 1 wk</td>
<td>No spasms and no hypsarrhythmia in 14 of 24 patients (58%)</td>
<td>21%</td>
</tr>
</tbody>
</table>

ACTH: Efficacy

- Other randomized controlled trials\(^1\)\(^-\)\(^4\)
  - Response rate: 42% to 80%
  - Relapse rate: 19% to 33%
- AAN/CNS practice parameter states that there is insufficient evidence on the optimum ACTH dose and duration of treatment for infantile spasms\(^5\)
  - High-dose study: 87% response rate\(^6\)
  - Low-dose study: 42% response rate\(^1\)
  - 2 studies found no dose-related difference in response rate\(^1\)\(^-\)\(^4\)
- Preponderance of evidence indicates that high dose is more effective than low dose

**ACTH: Relapse Rates**

- Relapse rates with high-dose ACTH
  - 15% reported by Hrachovy et al, 1994
  - 47% reported by Snead et al, 1983 (62% with prednisone)
  - 33% reported by Snead et al, 1989

- Relapse rates with low-dose ACTH
  - Hrachovy et al
    - 19% with low-dose ACTH vs 17% with PR (1983)
    - 21% with low-dose ACTH vs 15% with high-dose ACTH (1994)
    - 20% with low-dose ACTH (1980)

- In responders, relapse rates do not appear to differ

---

**ACTH: Relapse Rates and Time to Treatment**

Relapse rates are a function of time to treatment

- Singer et al, 1980
  - 51 patients treated with ACTH (80 U QOD)
  - Response rate
    - Treatment with ACTH within the first month of onset of spasms produced a higher incidence of spasm-free state and a shorter duration of spasms compared with a similar regimen of ACTH begun after seizures had persisted for more than a month.
  - Relapse rates
    - 3.7% for infants treated within 1 month of spasm onset
    - 21.4% for infants treated after 1 month of infantile spasms diagnosis

- Sher et al, 1993
  - 26 patients treated with ACTH (40-129 U/m²/d)
  - Response rate: 65% of patients (17 out of 26)
  - Relapse rates
    - 1 relapse of spasms during the initial withdrawal of medication;
      1 infant experienced a “recurrence” of infantile spasms many months later

- Early treatment with high response rates and low relapse rates

---

**ACTH: Cognitive Outcomes**

Favorable cognitive outcomes

- ACTH is the only drug treatment for which long-term outcomes are available
  - In cryptogenic cases treated early, there is a high rate of long-term normal outcome
    - Normal is defined as normal intelligence and no seizure disorder, on no medications
    - This is really NORMAL
  - No other drug can make this claim

---
Oral Corticosteroids

- There is insufficient evidence that oral corticosteroids are effective in the treatment of infantile spasms\(^1\).
- Even if there is some efficacy, oral corticosteroids are clearly inferior to high-dose ACTH\(^2\).
- Prednisone trials
  - 2 randomized controlled
  - 2 prospective open-label
  - 1 retrospective case study


Low-dose ACTH Versus Prednisone (1983)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
<th>Regimen</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>n=12</td>
<td>20 U/d IM for 2 wk (highest dose of ACTH was 30 U/d)</td>
<td>No spasms and no hypsarrhythmia in 42% (5 of 12) of patients</td>
</tr>
<tr>
<td>Prednisone</td>
<td>n=12</td>
<td>2 mg/kg per day for 2 wk</td>
<td>No spasms and no hypsarrhythmia in 33% (4 of 12) of patients</td>
</tr>
</tbody>
</table>


Oral Corticosteroids

- Randomized controlled trials: Baram et al, 1996
  - Prednisone 2 mg/kg for 2 to 6 weeks\(^1,2\)
  - Cessation of spasms in 29\% (2-week trial) and 33\% (6-week trial) of patients\(^1,2\)
  - Relapse rate was 13\%\(^1\)
- Response rate using prednisone was no different from that which might be expected from no treatment or placebo\(^3\)

Spontaneous Cumulative Remission Rates

ACTH and Oral Corticosteroids: Adverse Effects

- Adverse events: class effects\(^1,2\)
  - Hypertension (0%-37%)\(^3-6\)
  - Irritability (37%-100%)\(^4-6\)
  - Infection (14%)\(^5,7\)
  - Cerebral atrophy: reversible (7%-62%)\(^3,6\)

ACTH Adverse Events

- Partikian and Mitchell, 2007
  - Retrospective chart review of 130 patients treated for infantile spasms with ACTH or other antiepileptic drugs (AEDs)
  - All 43 patients who were treated with ACTH were treated with the high-dose regimen of 150 U/m² per day, divided BID for 2 weeks
- Major AEs were experienced by
  - 33% (6 of 18) of patients treated with other AEDs
  - 23% (14 of 60) of ACTH-treated patients
  - 15% (3 of 34) of vigabatrin-treated patients
  - None of the patients treated with prednisone
    - 60% (9 of 15) of prednisone-treated patients had their medication changed because of persistent infantile spasms
- None of the patients treated with ACTH required a change in medication because of weight gain or hypertension associated with end-organ damage

Hormonal Therapy vs Vigabatrin

- UK Infantile Spasms study comparing vigabatrin with hormonal therapy with vigabatrin
  - Primary outcome was clinical cessation of spasms
- Minimum doses
  - Tetracosactide (ACTH analogue), 40 U QOD IM (n=25)
  - Prednisone, 40 mg per day (n=20)
  - Vigabatrin, 100 mg per day (n=52)
- Efficacy
  - Hormonal therapy, 73% (40/55)
  - Vigabatrin, 54% (28/52), \( P = 0.04 \)
- Cognitive outcomes in cryptogenic cases at 12-14 months
  - Vineland scales
    - Hormonal therapy mean=88
    - Vigabatrin therapy mean=7%, \( P = 0.025 \)


Synthetic ACTH Tetracosactide vs Natural ACTH

![Graph showing mean plasma cortisol levels over time for different doses of Tetracosactide and 80 U ACTH1-39.]


Why and How Do ACTH and Glucocorticoids Work?

- “All-or-none”
- Within days
- Often no recurrence on treatment withdrawal

How Does ACTH Work?

We believe that high-dose ACTH works in 2 ways:

1. Release of natural corticosteroids from adrenals (low-dose ACTH is sufficient)
2. Direct penetration into the brain: action on melanocortin receptors, which reduces the levels of the excitatory brain stress hormone CRH. For this, very high doses are needed: poor BBB penetration

ACTH

Conclusions

Vigabatrin for Infantile Spasms

John M. Pellock, MD
Professor and Chairman,
Division of Child Neurology
Virginia Commonwealth
University/Medical College of Virginia Hospitals
Richmond, Virginia
Vigabatrin (VGB)

- Approved August 2009 for treatment of infantile spasms (IS) (orphan drug status)
  - Only drug approved in the US for treatment of IS
- Approved August 2009 for treatment of patients with refractory complex partial seizures who have responded inadequately to several antiepileptic drugs
- Previously approved years ago in other countries for partial seizures and utilized worldwide for the treatment of IS

Chemical Structure of VGB

Vigabatrin

\[ \text{Vigabatrin} \]

\[ \text{GABA} \]

VGB: Unique Mechanism of Action

VGB selectively and irreversibly inhibits GABA-T

- Increases number of GABA molecules at synapse
- Decreases seizure activity
VGB

- Specific, irreversible inhibitor of GABA-transaminase
  - Increases brain GABA levels
- Serum t½ is 5-7 hours but serum levels do not correlate well with efficacy
  - Biologic half-life is days
- No protein binding, no metabolism, no hepatic induction

VGB in Patients With IS

- 2-week, randomized, single-masked, multicenter trial
- Children <2 years of age with diagnosis of IS less than 3 months
- Randomized to receive low dose (18-35 mg/kg/d) or high dose (100-148 mg/kg/d)
- Most common side effects: sedation (42/167), insomnia (15/167), and irritability (15/167)
  - 9 patients (6.3%) discontinued therapy due to AEs
  - Visual fields unable to be assessed


Treatment Responders by VGB Dose and Etiology

<table>
<thead>
<tr>
<th>VGB Dose</th>
<th>Etiology</th>
<th>% Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Tuberous Sclerosis</td>
<td>11% (75)</td>
</tr>
<tr>
<td></td>
<td>Dysegnetic</td>
<td>36% (67)</td>
</tr>
<tr>
<td></td>
<td>Postratal</td>
<td>52% (24)</td>
</tr>
<tr>
<td>High</td>
<td>Tuberous Sclerosis</td>
<td>10% (25)</td>
</tr>
<tr>
<td></td>
<td>Dysegnetic</td>
<td>10% (21)</td>
</tr>
<tr>
<td></td>
<td>Postratal</td>
<td>10% (41)</td>
</tr>
<tr>
<td></td>
<td>Diolpethic or Cryptogenic</td>
<td>27% (45)</td>
</tr>
</tbody>
</table>

VGB Treatment of IS

Percentage of nonresponders among patients with tuberous sclerosis (dashed line) vs other etiologies (dotted line)


VGB for IS

In other randomized controlled studies:
- Symptomatic responders: 21% to 44%1-3
  - Tuberous sclerosis (5 prospective studies)1,3-6
    - Overall cessation of spasms: ~91%
    - 100% response rate reported
  - Cryptogenic responders: 27% to 57%1,3
- Relapse rate: 8% to 20%1-3


VGB: Adverse Effects

- Intramyelinic edema
- Psychosis
- Visual field defects
- Infantile MRI changes
VGB and Visual Field Defects

- Prevalence in adults: ~30% to 50%
  - May be less in infants
- Concentric constriction (average peripheral field= 65°; normal=90°); central vision not affected
- Typically asymptomatic
- Earliest occurrence: ~11 months
- Appears irreversible, but does not progress
- Appears idiosyncratic, not clearly dose related


<table>
<thead>
<tr>
<th>Degrees in the Temporal Visual Field of Final Goldmann Perimetry</th>
<th>Percentage of Patients Retaining X Degrees in the Temporal Visual Fielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>8.7</td>
</tr>
<tr>
<td>20</td>
<td>8.6</td>
</tr>
<tr>
<td>25</td>
<td>8.7</td>
</tr>
<tr>
<td>30</td>
<td>8.7</td>
</tr>
<tr>
<td>35</td>
<td>8.4</td>
</tr>
<tr>
<td>40</td>
<td>1.1</td>
</tr>
<tr>
<td>45</td>
<td>1.0</td>
</tr>
<tr>
<td>50</td>
<td>2.9</td>
</tr>
<tr>
<td>55</td>
<td>5.1</td>
</tr>
<tr>
<td>60</td>
<td>6.5</td>
</tr>
<tr>
<td>65</td>
<td>12.8</td>
</tr>
<tr>
<td>70</td>
<td>12.8</td>
</tr>
<tr>
<td>75</td>
<td>18.8</td>
</tr>
<tr>
<td>80</td>
<td>14.8</td>
</tr>
<tr>
<td>85</td>
<td>9.0</td>
</tr>
<tr>
<td>90</td>
<td>11.8</td>
</tr>
</tbody>
</table>

The percentage of patients (N=275) retaining various degrees (15° to 90°) of visual field in the temporal visual field of final Goldmann perimetry in the Aventis 4020 study. Right and left eye degrees were averaged. Masked ophthalmologists conducted the Goldmann visual field perimetry (Ovation Pharmaceuticals, Inc., 2007b).

aLeft and right eye degrees are averaged and rounded to the nearest 5 degrees.


Prevalence, Incidence, Earliest Time of Onset, and Mean Time of Onset of the VGB-induced Peripheral VFD in Adults and Children With CPS, and in Infants With IS

<table>
<thead>
<tr>
<th>Study 4020 Final Analysisa (n=524)</th>
<th>Glasgow Study (N=105)</th>
<th>Toronto Studya,b (N=197)</th>
<th>Kinross Study (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed VFD</td>
<td>Children: 15.3%</td>
<td>Adults: 30%-50%</td>
<td>Infants sustained abnormality: 30-Hz flicker amplitude=10.6% Cone b-wave amplitude=14.7%</td>
</tr>
<tr>
<td></td>
<td>Adults: 24.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong> (number of cases per 100 patient-years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed VFD</td>
<td>Children: 6.1</td>
<td>Adults: 4.4</td>
<td>Infants sustained abnormality: 30-Hz flicker amplitude=15.1 Cone b-wave amplitude=9.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Earliest Time of Onset</strong></td>
<td>First conclusive VFD</td>
<td>Adults: 11 months</td>
<td>Infants sustained abnormality: 9.9 months Adults: 1.1 years</td>
</tr>
<tr>
<td></td>
<td>Children: 11 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Confirmed visual field defect (VFD): ≥2 abnormal visual fields that were categorized as bilateral concentric peripheral constriction; sustained abnormality: ≥2 abnormal electroretinography (ERG) findings based upon the 30-Hz flicker amplitude first conclusive VFD: appearance of the bilateral concentric peripheral constriction at first viable perimetry.
Testing Options for Peripheral Visual Field Defect

<table>
<thead>
<tr>
<th>Testing Options</th>
<th>8 Years and Older*</th>
<th>12 Years and Older*</th>
<th>12 Years and Older*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroretinography (ERG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The only testing option appropriate for infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uses an electrode placed on the eye to monitor electrical activity in the retina in response to a flash of light</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confrontation Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examiner moves hand through patient’s peripheral visual field to roughly determine the border of the visual field</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic Perimetry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examiner moves stimuli through patient’s peripheral vision and maps visual field defects on a reference grid (Goldmann perimetry testing is an example of kinetic perimetry)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automated Perimetry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uses automated visual field analyzers, such as Octopus and Humphrey visual field analyzers, to project light stimuli, measure reaction, and map the patient’s visual field</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An objective testing option

More sensitive than confrontation testing, but also more challenging to perform and less widely available

Widely available and easily performed, but not a sensitive test

Uses automated visual field analyzers, such as Octopus and Humphrey visual field analyzers, to project light stimuli, measure reaction, and map the patient’s visual field

Examiner moves stimuli through patient’s peripheral vision and maps visual field defects on a reference grid

Examiner moves hand through patient’s peripheral vision to roughly determine the border of the visual field

An objective testing option that usually requires sedation in infants and young children

An objective testing option that usually requires sedation in infants and young children

Ages ranges are estimates. Cognitive abilities should be taken into consideration.

Willmore et al, 2009

Visual Field Defects at School Age in Children Treated With VGB in Infancy

- N=16; IS; mean onset, 7.6 months
- Therapy duration, 21 months (9.3-29.8)
- Cumulative dose, 655 g
- VF by Goldman Perimetry at 6 to 12 years of age
- Normal visual fields in 15/16
- Conclusion: Risk of VA VFL may be lower when treated as infants (vs 20%-40%)

Cerebral MRI Abnormalities Associated With Vigabatrin Therapy

Purpose: Investigate whether patients on vigabatrin demonstrated new-onset and reversible T2-weighted magnetic resonance imaging (MRI) changes.

Methods: MRI of patients treated during vigabatrin therapy was reviewed, following detection of new basal ganglia, thalamic, and corpus callosum hyperintensities in an infant treated for infantile spasms. Patients were assessed for age at time of MRI, diagnosis, duration, and dose, MRI findings, age, and post-vigabatrin, concurrent medications, and clinical correlations. These findings were compared to MRI in patients with infantile spasms who did not receive vigabatrin.

Results: Thirteen patients were identified as having MRI changes during the course of vigabatrin therapy. After excluding the two cases, we discussed new and reversible basal ganglia, thalamic, or corpus callosum abnormalities in 7 of 12 (58%) patients treated with vigabatrin. All findings were reversible following discontinuation of therapy. Diffusion-weighted imaging (DWI) was positive with apparent diffusion coefficient (ADC) maps demonstrating restricted diffusion. Affected areas included basal ganglia, thalamus, and Corpus Callosum, with a mean age of 11 months versus 3 years, therapy duration 3 months versus 13 months, and dosage 13 mg/kg versus 1 mg/kg. All affected patients were treated for infantile spasms; none of 16 patients with infantile spasms who were not treated with vigabatrin showed the same abnormalities.

Conclusions: MRI abnormalities attributable to vigabatrin, characterized by new-onset and reversible T2-weighted hyperintensities and restricted diffusion, were found in 58% of the cases. Basal ganglia, thalamus, or corpus callosum were identified in 9 of 12 patients. Young age and relatively high doses appear to be risk factors.

Keywords: Vigabatrin, MRI, Infantile spasms.
VGB-associated MRI Abnormalities

- 332 MRIs/205 infants
- Abnormal defined as any hyperintensity on T2 or Flair
- 22% vs 4% (VGB vs naive), P<0.001
- Resolution in 6/9 prevalent with repeat study
  - VGB discontinued in 4
- Conclusions: VGB associated with transient, asymptomatic MRI abnormality in IS infants. Majority resolved (w/wo VGB discontinuation)

Summary: MRI Abnormalities

- Characteristic locations: brainstem, cerebellum, basal ganglia, and thalamus
- Approximately 6-fold greater relative risk with VGB exposure (10%-20%)
- Possible dose-dependent effect (NS)
- No additional risk factors identified
- Resolved on follow-up MRI in 7 of 12 patients
  - After discontinuation or with ongoing VGB
- No associated clinical sequelae observed
Early Onset of Efficacy Allows for Early Identification of Patients Who Benefit

<table>
<thead>
<tr>
<th>Evaluation Phase</th>
<th>Maintenance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset within 2 weeks</td>
<td>Ongoing ophthalmologic testing, patient assessment, and treatment</td>
</tr>
</tbody>
</table>

- Initiate therapy
- Perform baseline ophthalmological test
- Earliest confirmed electrophysiologic change underlying pVFD in 18 months

---

**Sabril (vigabatrin) for Oral Solution**

For Oral Administration Only
Initial U.S. Approval: 2000

**WARNING: VISION LOSS**
See full prescribing information for complete boxed warning
- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known to be free of risk of vision loss.
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL.
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage.
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program.

---

**Comprehensive Risk Evaluation and Minimization Plan (REMS)**

- Appropriate patient selection through education and attestation
- Controlled distribution through specialty pharmacies

**Physician**
- Share
- Welcome kit and reminder for VF testing

**Starter Kit**
- Patient/ Caregiver
- Ophthalmologic Testing Every 6 Months

**Specialty Pharmacy**
- Review kit
- Sign agreement
- Receive Rx

---
VGB Oral Solution for IS Dosing

- Initiate therapy at 50 to 150 mg/kg/d given BID
- Powder for oral solution, 500 mg (10 mL)

VGB Treatment of IS

- Efficacy established, especially TS
- Defined MOA
- Safety concerns
  - Vision
  - MRI changes
- REMS program

Treatment of Infantile Spasms: Efficacies of Other Available Therapies

Tracy Glauser, MD
Professor of Pediatrics
Director, Comprehensive Epilepsy Center
Cincinnati Children’s Hospital Medical Center
Cincinnati, Ohio
Leeches
Cold applications
Calomel purgatives
Gums lanced
Warm baths
Sedatives
Syrup of poppies, conium, and opium
Castor oil

Current Treatment Options
(Other Than ACTH or Vigabatrin)

- Pharmacological therapies
  - Randomized controlled trial (RCT) evidence
  - Case series
- Dietary therapies
- Surgical treatments

Pharmacological Therapies
(RCT Evidence)

Valproic acid
- Placebo (PLB), crossover design (N=17)
- Mean spasm index: VPA>PLB (P<0.04)

Nitrazepam (NTZ)
- Parallel group, 4 weeks, ACTH comparator
- NTZ (n=27), ACTH (n=25)
- >50% spasm reduction: NTZ, 66%; ACTH, 50%

Sulthiame
- Parallel group, PLB, 9 days
- SLT 5-10 mg/kg/day (n=28), PLB (n=23)
- Spasm free: SLT, 8/28; PLB, 1/23 (OR, 5.13; 95% CI, 0.7-5.9)
Pharmacological Therapies
(Case Series Evidence)

- Pyridoxine
- Felbamate
- Lamotrigine
- Topiramate
- Levetiracetam
- Zonisamide
- Ganaxolone
- Thyrotropin-releasing hormone
- Intravenous immunoglobulin

AED | Dose | Spasm Freedom
---|---|---
Pyridoxine | 10-50 mg/kg/day (up to >1 g/day) | 35%-40% cryptogenic
Felbamate | 15-45 mg/kg/day | 3/4 in one study
Lamotrigine | 5 mg/kg/day (if with VPA) | 17% in one study
 | 15 mg/kg/day (if not with VPA) | 
Topiramate | Up to 27 mg/kg/day | 18%-45% spasm free
Levetiracetam | Up to 30 mg/kg/day | 40% in one study
Zonisamide | Up to 20 mg/kg/day | 22%-36%
Pharmacological Therapies (Case Series Evidence)

<table>
<thead>
<tr>
<th>AED</th>
<th>Dose</th>
<th>Spasm Freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganaxolone</td>
<td>Up to 36 mg/kg/day</td>
<td>5% in one study</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
<td>0.5-1 mg/day for 1-4 weeks</td>
<td>54% in one study</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>100-200 mg/kg every 2-3 weeks</td>
<td>64% in one study</td>
</tr>
<tr>
<td></td>
<td>1 g/kg q3wk for 6 months</td>
<td>22% in one study</td>
</tr>
</tbody>
</table>

Dietary Therapies: Ketogenic Diet

- Prospective, 1994-1996 (N=13)
  - Seizure free, 8% (1/13); >90% 31% (4/13)
- Retrospective, 1983-1997 (N=17)
  - Seizure free, 35% (6/17)
- Retrospective, 1996-2000 (N=23)
  - Average of 3.3 AEDs
  - 17 failed/relapsed with ACTH/steroids
  - Johns Hopkins Hospital protocol

Dietary Therapies: Ketogenic Diet

Results (%): Seizure Free, >90%, 50%-90%

<table>
<thead>
<tr>
<th>Months of Therapy</th>
<th>(n=21)</th>
<th>(n=18)</th>
<th>(n=15)</th>
<th>(n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results (%)</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>

### Dietary Therapies: Ketogenic Diet

**Factors that predicted >90% seizure reduction at 12 months:**
- Age at diet initiation (<1 year) \( P=0.02 \)
- Exposure to \( \leq 3 \) AEDs \( P=0.03 \)
- Absence of hypersarrhythmia \( P=0.07 \)

**Factors that were not predictive**
- Cryptogenic vs symptomatic cause
- Prior seizure frequency, ketogenic diet ratio

---

### Dietary Therapies: Ketogenic Diet – First-line Therapy?

- KD \( (n=13) \) vs ACTH \( (n=20) \) as initial therapy
- Retrospective, nonrandomized
- After 1 month of therapy
  - Spasm freedom
    - KD, 62% \( (8/13) \) vs ACTH, 90% \( (18/20; P=0.06) \)
    - Normal EEG
      - ACTH, 53% \( (9/17) \) > KD, 9% \( (1/11; P=0.02) \)
- No difference in relapse
- Adverse events (6 months)
  - KD, 31% \( (4/13) \) < ACTH, 80% \( (16/20; P=0.006) \)

---

### Resective Epilepsy Surgery in Infantile Spasms

<table>
<thead>
<tr>
<th>Failed Medical Therapy (B_{6}, ACTH, VGB)</th>
<th>Surgical Candidates</th>
<th>Not Surgical Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exam</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Development</td>
<td>May be focal</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Normal/lesion</td>
<td>Diffuse lesion/normal</td>
</tr>
<tr>
<td>EEG (II, I)</td>
<td>Focal abnormality</td>
<td>Independent, bilateral</td>
</tr>
<tr>
<td></td>
<td>Partial onset seizures</td>
<td>Seizure onset</td>
</tr>
<tr>
<td>PET</td>
<td>Ulnar abnormality</td>
<td>Diffuse or multifocal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypometabolism</td>
</tr>
</tbody>
</table>
Resective Epilepsy Surgery in Infantile Spasms

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Institution</th>
<th>Number</th>
<th>Mean Follow-up (Month)</th>
<th>Seizure-free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chugani, 1993</td>
<td>UCLA</td>
<td>23</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>Kramer, 1997</td>
<td>Harvard</td>
<td>9</td>
<td>34</td>
<td>67</td>
</tr>
<tr>
<td>Wyllie, 1998</td>
<td>Cleveland</td>
<td>2</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Hoffman, 2002</td>
<td>Toronto</td>
<td>11</td>
<td>-</td>
<td>45</td>
</tr>
</tbody>
</table>

Surgical Treatment of Infantile Spasms

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>Tumor (n=2)</th>
<th>TSC (n=2)</th>
<th>Hemispherectomy (n=21)</th>
<th>Other (n=4)</th>
<th>Lobar Resection (n=6)</th>
<th>Multilobar Resection (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4%</td>
<td>4%</td>
<td>41%</td>
<td>8%</td>
<td>12%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Pathology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical dysplasia</td>
<td>32</td>
</tr>
<tr>
<td>Infarction</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
</tr>
<tr>
<td>TSC</td>
<td>3</td>
</tr>
<tr>
<td>Tumor</td>
<td>2</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>4</td>
</tr>
</tbody>
</table>
Surgical Treatment of Infantile Spasms

Outcome

Patients (%)

Class:
- Seizure Free
- <1/ Month
- 1-4/ Month
- 5-30/ Month
- >30/ Month


Surgical Treatment of Infantile Spasms

Seizure Recurrence After Surgery

Maintaining Complete Seizure Control (%)

Months After Surgery


Surgical Treatment of Infantile Spasms

Developmental Outcome

- Significant improvement on postsurgical scales
  - Communication skills
  - Daily living skills
  - Socialization
  - Adaptive behavior composite
- Best postoperative results
  - Children with best preoperative DQ
  - Younger children

## Conclusions

- There are medical, dietary, and surgical treatment options for patients with infantile spasms other than ACTH or vigabatrin
- Patients can achieve seizure freedom with these other therapies
- Limited rigorous evidence exists regarding the efficacy of these therapies