ALGORITHMS IN THE DIAGNOSIS AND TREATMENT OF SEIZURES, SEIZURE EMERGENCIES, AND EPILEPSY

POWERPOINT PRESENTATIONS

January 23–25, 2015 • Phoenix, AZ

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2015 AAN Breakthroughs in Neurology Conference
January 23-25, 2015
Algorithms in the Diagnosis and Treatment of Seizures, Seizure Emergencies, and Epilepsy
Friday, January 23, 2015
8:00 a.m. – 11:00 a.m.
CME Credits: 3

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- CME Credits/Certificates of Attendance will be sent to attendees four to six weeks following the Regional Conference.

Program Director
Joseph I. Sirven, MD, FAAN
Scottsdale, AZ

Program Schedule and Faculty

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<td>8:00 a.m. – 8:05 a.m.</td>
<td>Introduction</td>
<td>Joseph I. Sirven, MD</td>
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<td>8:05 a.m. – 8:50 a.m.</td>
<td>Algorithms in Diagnosing Spells as Seizures and Epilepsy</td>
<td>Amy Crepeau, MD</td>
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<td>8:50 a.m. – 9:30 a.m.</td>
<td>Algorithms in Managing Epilepsy: AEDs: Choosing, Titrating, Monitoring and Withdrawal</td>
<td>R. Edward Hogan, MD</td>
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<td>St. Louis, MO</td>
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<td>9:30 a.m. – 9:40 a.m.</td>
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<td>9:40 a.m. – 10:20 a.m.</td>
<td>Algorithm in Treating Patients with Drug Resistant Epilepsy: Lesional and Nonlesional</td>
<td>John M. Stern, MD</td>
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<td>Los Angeles, CA</td>
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<td>10:20 a.m. – 11:00 a.m.</td>
<td>Algorithm in Treating Seizure Emergencies: Acute Seizure, Seizure Clusters and Status Epilepticus</td>
<td>Joseph I. Sirven, MD</td>
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Program Description:
With a large armamentarium of diagnostic tools and therapeutic options that span 28 drugs, multiple surgeries, diet, devices and psychosocial treatments, the diagnosis and management of seizures and epilepsy has evolved to a complex set of clinical decisions. These choices hold important ramifications for the patient with seizures, epilepsy or a seizure emergency.

This course helps to distill the essence of the fundamental clinical decisions that are made with patients with...
acute seizures and epilepsy. Through a series of case presentations, the faculty will present and show the latest clinical algorithms pertaining to important clinical consultations in the field including: diagnosis of seizures and epilepsy; when to start an anti-seizure drug and how to choose among several different compounds; when to diagnose a patient as drug resistant with consideration for surgical management or devices and/or diet; and how to handle seizure emergencies and status epilepticus.

Learning Objectives:
To present algorithms on the best approach to manage the following common yet vexing clinical seizure and epilepsy problems:
1. Diagnosing a seizure and epilepsy
2. Choosing the best seizure drug and how to titrate and monitor therapy for best results
3. Diagnosing and treating drug resistant epilepsy - what to do
4. Diagnosing and Treating Seizure Emergencies

Recommended Audience:
General Practitioner, Epileptologist

Core Competencies:
Practice-based Learning and Improvement

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

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Faculty Commercial Relationship Disclosures
- Dr. Sirven has received personal compensation for activities with Upsher Smith. Dr. Sirven has received personal compensation in an editorial capacity for epilepsy.com. Dr. Sirven has received research support from Neuropace Inc.
- Dr. Crepeau has nothing to disclose.
- Dr. Hogan has received personal compensation for activities with Upsher Smith as a consultant. Dr. Hogan has received research support from Eisai Inc. and Upsher Smith.
Dr. Stern has received personal compensation for activities with Lundbeck, Sunovian, Cyberonics, Upsher Smith, and UCB Pharma. Dr. Stern has received personal compensation in an editorial capacity for MedLink.

Unlabeled Use of Product Disclosure
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Faculty Unlabeled Use of Product Disclosures
- Dr. Sirven will discuss investigational products for the treatment of seizure clusters.
- Dr. Crepeau will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Hogan will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Stern may discuss Deep Brain Stimulation for epilepsy.
Algorithms in Diagnosing Spells as Seizure and Epilepsy

Amy Z. Crepeau, M.D.
Mayo Clinic
Phoenix, Arizona

Disclosures

• None
Objectives

• Outline semiologic features of different seizure types.
• Discuss the initial work-up to look for evidence of epilepsy.
• Identify additional testing that can be performed to clarify diagnosis of epileptic vs. nonepileptic spells.
• Review the utility of ancillary testing to diagnosis nonepileptic spells.

Definitions

• Epileptic Seizure
  • Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

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

ILAE, 2014
Case 1

• A 51 year-old right-handed female is referred to Neurology clinic for evaluation of spells. These spells have been occurring over approximately the last year.

• At the time of onset, she was under stress due to her daughter’s legal troubles, but otherwise, there was no obvious provoking factor.

• She has no history of neurologic illness or injury.

• She reports the spells have been stereotyped in their semiology.

• The events begin with a “weird sensation over my body”. This lasts for one minute and either resolves, or progresses such that “I’m just not there”. Her husband reports at this point, she does not speak and seems to be nonresponsive. This may last another minute. She has no recall as to what happens during this time.
• She has no history of other unusual spells, febrile seizures, CNS infections, significant head traumas or family members with seizures.

• Past medical history is remarkable only for anxiety and depression.

Evaluating a Patient with Spells

• Description of events
  • How many types?
  • Stereotyped or variable?
  • Warning?
  • Patient and witness accounts
  • Are there focal features?
  • Post-ictal state?
  • Nocturnal, diurnal, or both?
  • Triggers?
  • Frequency
  • Duration
• Additional History
  • Epilepsy risk factors
    • Febrile seizures
    • CNS infections
    • Significant head trauma
    • Family history of seizures/epilepsy
  • Past medical history
  • Neuroimaging
  • Prior EEGs

Spells

Seizures
  • Focal
    • Temporal
    • Extratemporal
    • Multifocal
  • Generalized

Non-epileptic events
  • Physiologic
    • Ischemic/Vascular
    • Cardiac
    • Autonomic
    • Sleep Disorder
    • Movement Disorder
    • Migraine
    • Encephalopathy
    • Medication
    • Metabolic
  • Behavioral
    • Conversion
    • Malingering
    • Panic attacks
Semiology

• Focal Seizures: Seizure onset zone determines semiology.
• Temporal Lobe Seizures
  • Slight female predominance.
  • Simple partial seizures typically last a few seconds, complex partial seizures are usually longer than 1 minute.
  • May be have history of febrile seizures in childhood.
  • Sensory Aura- Olfactory, gustatory hallucinations. Epigastric rising. Auditory hallucinations (likely lateral temporal).
  • Experiential- Psychic feeling, déjà vu, depersonalization, fear, panic.
  • Autonomic- Flushing, nausea, pallor.
  • Aphasia.
  • Typically followed by postictal confusion, fatigue, with gradual recovery.

• Video 1.mpg
• Frontal Lobe Seizures
  • Slight male predominance.
  • Often will have clusters of nocturnal seizures.
  • Brief in duration, but can quickly secondarily generalize.
  • May have somatosensory aura, “Jacksonian march”, early posturing or clonic activity, “bicycling”.
  • May be “hypermotor”- large amplitude, irregular, complex movements.
  • Autonomic features due to insular involvement.
  • Orbitofrontal seizures can mimic temporal lobe seizures.
  • Very brief postical phase.

• Video 2.m4v
• Parietal Lobe Seizures
  • Aura is typically sensory with tingling or electrical feeling.
  • Negative sensory feelings consist of numbness or asomatognosia.
  • Patients may have an urge to move.
  • Formed visual hallucinations.

• Occipital Lobe Seizures
  • Visual symptoms- elemental.
  • Distorted vision.
  • Migraine?
Generalized Seizures

• Generalized Tonic-Clonic
  • Prodrome may precede seizure by up to 2 days- changes in mood, cognition or perception.
  • Often begins with ictal cry, immediately into generalized tonic phase.
  • No consistent head deviation or posturing.

• Video 4.mpg
• Absence
  • No warning.
  • Duration under 30 seconds with rapid recovery.
  • Rarely de novo onset in adults.
  • Absence status epilepticus can occur in adults, with a predisposition to generalized seizures, in the setting of benzodiazepine or alcohol withdrawal, psychotropic drugs.

• Myoclonic Seizures
  • Single, brief jerks, but often cluster.
  • May involve any or all limbs, torso.
  • Typically occur along with other generalized seizures.
  • Not all myoclonus is seizure!
• Tonic
  • More typically occurs in setting of symptomatic generalized epilepsy.
  • Brief, may fall backwards
• Atonic
  • More typically occurs in setting of symptomatic generalized epilepsy.
  • Head drop, fall forward.
Features Suggestive of Non-Epileptic Behavioral Events

- Long duration (greater than 3 minutes)
- Variable onset
- Waxing and waning motor activity
- Entire body convulsions with maintained awareness
- Eyes closed, with resisted eyelid opening
- Opisthotonic posture
- Side to side head movements
- Nonphysiologic progression
- Directly provoked by stressful situations
- History of psychiatric disease

- Video 5.mpg
Initial Evaluation

Neuroimaging

- In evaluating indeterminate spells, neuroimaging is performed to look for underlying structural abnormalities which may indicate a seizure focus.

- CT
  - Readily available, short scanning time.
  - Able to detect large structural or vascular lesions.
  - Limited sensitivity for small cortical lesions, mesial temporal structures.
  - Success of detecting lesions in focal epilepsy is 30.3%.
• MRI
  • “Gold standard” for imaging in evaluation of epilepsy.
  • Able to distinguish well between gray and white matter.
  • Excellent at visualizing mesial temporal structural, cortical abnormalities.
  • Location of structural abnormalities needs to be correlated with clinical description of events!
  • 3T increases yield of detecting subtle cortical abnormalities.

• PET
  • 18F-fluorodeoxyglucose is injected to look for regions of relative hypometabolism (interictal state).
  • 18F-FDG uptake may be increased in the ictal state.
  • In MRI-negative temporal lobe epilepsy, focal hypometabolism is predictive of seizure freedom after temporal lobectomy.

Case 2

• A 50 year-old gentleman is referred to Epilepsy Clinic by his new primary care physician due to a poorly defined prior history of epilepsy.
• The patient reports a life-long history of stereotyped spells.
  • Events begin with a sensation he is driving quickly down a steep hill, followed by itching of the left palm. His wife reports he has a brief smile and laugh, which is different than his normal, spontaneous laugh. He does not lose awareness.
• These can up to 6 times per day.
• He has never had a convulsion.
• Seizure risk factors: No history of febrile seizures, CNS infections, significant head trauma, or family members with seizures.

• Medical History significant for Tourette’s syndrome.

• Outpatient EEG shows mild, intermittent left hemispheric slowing, no epileptiform activity.
Case 3

• A 78 year-old gentleman is referred to Neurology Clinic after a first time seizure.

• The seizure began with left arm jerking, which spread to the left face, and then secondarily generalized. The seizure lasted approximately 90 seconds, and he began responding again after approximately 3 minutes.

• A significant seizure risk factor is a right middle cerebral artery infarction, which occurred approximately 6 months prior to the seizure. He had residual left sided weakness, dysarthria and dysphagia, and was continuing with outpatient physical therapy.

• Outpatient EEG shows moderate diffuse background slowing, which is maximal over the right hemisphere.
Electroencephalography

- American Academy of Neurology Practice Management Guidelines recommend outpatient EEG as part of the evaluation of an adult with first-time seizure.
- 29-55% of initial EEGs after a first seizure show epileptiform activity.
- Epileptiform activity after a first time seizure is associated with seizure recurrence rates of 30-70% at one year.
- The rate of epileptiform activity in healthy volunteers is between 0-6.6%.
- Hyperventilation, photic stimulation and sleep deprivation increase yield of epileptiform activity.
Caveats....

- 40% of patients eventually diagnosed with epilepsy will have no epileptiform activity on the initial EEG.
- Patients with extratemporal onset focal epilepsy are less likely to have interictal epileptiform discharges.
- Occipital spikes have been reported in blind individuals without epilepsy.
- First degree of relatives of patients with generalized epilepsy may have generalized epileptiform discharges.
- Beware of normal variants which may be confused for epileptiform activity!
  - Wicket waves
  - Sawtooth waves
  - RTTD

Case 4

- A 19 year-old college student is referred to your clinic for a witnessed generalized tonic-clonic seizure.

- He was in the college gym at the time of the seizure, feeling well, with no recall of an aura. Witnesses report he suddenly made a noise, fell to the ground, and had generalized convulsions lasting approximately 60 seconds. He was confused and amnestic to events for approximately 15 minutes afterwards.

- There were no obvious provoking factors including drug or alcohol use, sleep deprivation or illnesses.
• In retrospect, he reports a 3 year history of funny spells.

• Spells consisted of a sudden “blood taste” in his mouth, and a feeling as though he was “in his own little world.” Friends had noticed him staring at times. It is unclear if he would lose awareness. These events have occurred nearly daily.

• MRI was performed and was normal.
Additional Testing Considerations

Outpatient Ambulatory EEG

• Advantages
  • Increases yield of epileptiform activity.
  • Increases yield of capturing habitual event.
  • Patient is in normal environment, with typical stressors, exposures, etc.

• Disadvantages
  • Variable video availability.
  • Limited technical quality.
  • Does not provide a safe environment to taper or discontinue AEDs.
  • Patient cannot be reliably assessed during event.
Inpatient Video EEG Monitoring

• Indications for Video EEG Monitoring
  • Spell classification
  • Seizure classification
  • Seizure localization
  • Seizure quantification
  • Medication adjustments under EEG monitoring
• Allows for tapering and discontinuation of AEDs in a controlled setting.
• Concurrent video, along with real-time clinical assessment, including vital signs, blood work, coincidental medications.

Utility of Video EEG Monitoring

• The yield of diagnosis for paroxysmal spells during admission is up to approximately 80%.
  • Diagnosis is based upon capturing a typical event or definitive interictal epileptiform activity.
• On average, 30% of spells are diagnosed as nonepileptic behavioral events.
• Physiologic nonepileptic events recorded include ischemia, syncope, sleep disorders and encephalopathy.
• Admission results in a change in the diagnosis in 40-60% of patients.
  • Approximately 20% of patients admitted for intractable epilepsy ultimately are shown to have nonepileptic events.
• Clinical Events without EEG correlate
  • Nonepileptic events
  • Very focal seizures without sufficient propagation for scalp correlate (simple partial seizures).
  • Extratemporal seizures without secondary generalization.

Case 5

• A 45 year-old woman was admitted to the Epilepsy Monitoring Unit for seizure localization and pre-surgical evaluation.

• She has a five year history of seizures, which have not been controlled despite a trial of 4 AEDs and a vagus nerve stimulator.

• At the time of admission, she had recently had an increase in seizure frequency.
Two types of events are described.

- The first event type begins with flashing lights and blurred vision. She then has a strong sense of “doom” and fear. She typically will then lose awareness and her husband reports she has a “blank look” and is unresponsive. These last approximately 45-60 seconds and occur 2-3 times per week.

- The second event type begins with flashing lights, and then an intense pressure in her head. She becomes nauseated. Her husband reports she then begins yelling and having irregular movements of all of her extremities. These events have increased in recent weeks, occurring nearly daily.

Video

- Video 6.wmv
Ictal SPECT Imaging

- Subtraction SPECT Co-registered to MRI (SISCOM)
  - Ictal injection is performed; SPECT shows hyperperfusion at seizure focus.
  - Interictal injection is performed; SPECT shows hypoperfusion at seizure focus.
  - Subtraction and co-registration provides localizing, lateralizing or indeterminate information.
- When there is no scalp correlate, localizing or lateralizing data can assist in diagnosis of epilepsy.
- Indeterminate findings on SISCOM, without EEG correlate, in an event suspected to be nonepileptic can be reassuring of nonepileptic etiology.
Neuropsychometric Testing

- Provides objective cognitive data which can localize areas of cerebral dysfunction.
- Temporal lobe epilepsy more likely to have lateralizing cognitive deficits.
- Personality assessments assist in identifying patients with a tendency for somatization.
- Validated scales for somatic complaints and conversions correlate with nonepileptic behavioral events.
Additional Testing Considerations

- Cerebrovascular Imaging
- Holter Monitor
  - Arrhythmias
- Autonomic Studies/ Tilt Table Test
  - Orthostatic Hypotension
  - Postural Orthostatic Tachycardia Syndrome (PoTS)
  - Autonomic Neuropathy
- Polysomnography
  - Parasomnias
  - Sleep apnea
- Movement Disorder Physiologic Study
  - Myoclonus
  - Tremor

Case 6

- A 24 year-old woman is referred to Epilepsy Clinic for seizures which have failed to respond to multiple AEDs.

- Seizures began 4 years ago, and have continued despite treatment with levetiracetam, lamotrigine and lacosamide.

- The seizures begin with tunnel vision and a “rising feeling” in her abdomen. She has difficulty understanding what people are saying to her. She then loses awareness and has generalized convulsions. Convulsions last 45-60 seconds. She reports regaining awareness fairly quickly, but fatigued for several hours afterwards.
• Seizure risk factors: No history of febrile seizures, CNS infections, significant head trauma or family members with seizures.

• Past medical history is significant for juvenile rheumatoid arthritis, which has been in remission for the past 2 years.

• Routine outpatient EEGs have been normal. Prior 4 day inpatient video EEG monitoring showed a normal EEG, but no events were captured.

Video

• Video 7.wmv
Spells

Seizures
- Focal
  - Temporal
  - Extratemporal
  - Multifocal
- Generalized

Non-epileptic events
- Physiologic
  - Ischemic/Vascular
  - Cardiac
  - Autonomic
  - Sleep Disorder
  - Movement Disorder
  - Migraine
  - Encephalopathy
  - Medication
  - Metabolic
- Behavioral
  - Conversion
  - Malingering
  - Panic attacks
Case 1 (revisted)

• A 51 year-old right-handed female is referred to Neurology clinic for evaluation of spells. These spells have been occurring over approximately the last year.
• At the time of onset, she was under stress due to her daughter’s legal troubles, but otherwise, there was no obvious provoking factor.
• She has no history of neurologic illness or injury.

• She reports the spells have been stereotyped in their semiology.
• The events begin with a “weird sensation over my body”. This lasts for one minute and either resolves, or progresses such that “I’m just not there”. Her husband reports at this point, she does not speak and seems to be nonresponsive. This may last another minute. She has no recall as to what happens during this time.
• She has no history of other unusual spells, febrile seizures, CNS infections, significant head traumas or family members with seizures.

• Past medical history is remarkable only for anxiety and depression.

Evaluation

• Outpatient EEG- Normal awake and asleep.

• MRI Brain- Normal.

• Neuropsychometric testing- Multifocal cognitive impairment, not strongly lateralizing. Personality assessment inventory invalid due to inconsistent answers, but patient presented as severely depressed and overwhelmed.
• Video EEG Monitoring captured 2 event types
  • Type 1: Reported abnormal feeling, oral automatisms, able to respond to questions appropriately. Tachycardia noted on EKG. EEG shows left temporal seizures.
  • Type 2: She stops responding to bystanders. When questioned, she follows simple commands. She then becomes tremulous and hyperventilated. EEG remains normal during these events.

Key Points

• A detailed description of the events and clinical history can assist in determining the likely diagnosis.

• Outpatient EEG and MRI should routinely be used to determine the likelihood of events being seizure.

• When the diagnosis is not clear, video EEG monitoring is the gold standard.

• Consider physiologic causes for nonepileptic events.
Algorithms in Managing Epilepsy: AEDs: Choosing, Titrating, Monitoring and Withdrawal

R. Edward Hogan, M.D.
Professor, Department of Neurology
Director, Adult Epilepsy Center
Washington University in St. Louis

Disclosure

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<td>Eisai and Upsher-Smith Pharmaceuticals</td>
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Overview

- Choosing
  - “traditional” vs. “new” antiepileptic medications
  - generics
- Titrating and Monitoring
  - seizure severity
  - levels
- Withdrawal

Choosing

- Summary of “traditional” and “new” AEDs
- Comparative studies and use of medication
- Issues with use of generic medications
Major Antiepileptic Drug (AED) Therapy in the U.S.

- AEDs approved before 1993 (traditional)
  - Phenobarbital, Phenytoin, Primidone, Carbamazepine, Valproate

- AEDs approved since 1993 (new)
  - Felbamate, Gabapentin, Lamotrigine, Topiramate, Tiagabine, Zonisamide, Oxcarbazepine, Levetiracetam, Pregabalin, Rufinamide, Lacosamide, Vigabatrin, Ezogabine, Clobazam, Eslicarbazepine


AEDs

- Partial onset seizures
  - carbamazepine, lamotrigine

- Most “new” AEDs are approved for partial seizures, some as “monotherapy,” some as “adjunctive therapy.”

- “Orphan” indications
Antiepileptic Drugs

• Generalized epilepsy
  – Valproate
  – Felbamate
  – Lamotrigine
  – Topiramate
  – Zonisamide
  – Levetiracetam
  – Rufinamide
  – Vigabatrin
  – Clobazam

VA Cooperative study (CS 118)

• Comparison of CBZ, PHT, PRM, and PB in patients with partial and 2º GTC seizures
• 622 adult patients over 6 years
• Primary evaluating variable was patient retention (length of time patients remained on the randomly assigned drug)

VA Cooperative study (CS 118)


Standard and New Antiepileptic Drug (SANAD) trial

- Unblinded randomization of patients with idiopathic generalized epilepsy to treatment with valproate, lamotrigine, or topiramate, with follow up from 2-5 years with 716 randomized subjects
- Assessment of time to treatment failure showed valproate was significantly better than topiramate or lamotrigine
- For time to 12-month remission valproate was significantly better than lamotrigine, but no different than topiramate

Standard and New Antiepileptic Drug (SANAD) trial

• Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalized and unclassified epilepsies. However, because of known potential adverse effects of valproate during pregnancy, the benefits for seizure control in women of childbearing years should be considered


Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

• Patients with newly diagnosed epilepsy who require treatment can be initiated on traditional AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs
• Choice of AED will depend on individual patient characteristics

“Traditional” and “new” AEDs

- None of the AEDs approved since 1993 have demonstrated better efficacy in treating partial epilepsy than the “traditional” AEDs
- Tolerability, side effect profiles and drug interaction profiles are better for some of the “new” AEDs
- Use of the currently available AEDs is guided by individual patient indications (seizure type, potential side-effects, cost, etc.)

ILAE defined drug-resistant epilepsy, with 2 “hierarchical” levels.

- Level 1
  - Assessment of adequate trial of AED for efficacy in treating seizures
- Level 2
  - drug-resistant epilepsy as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens to achieve freedom from seizures.
  - if complete seizure control is not achieved with trials of two appropriate antiepileptic drugs, the likelihood of success with subsequent regimens is much reduced
  - while drug resistance may “remit” over time (at a rate of 4% per year among adults and a higher rate among children), seizure relapse is common, suggesting a fluctuating course.

Responder rates (50% seizure reductions) as a function of newly administered AEDs failed due to lack of efficacy or adverse events

New AEDs

- A significant number (20-30%) of patients with epilepsy will not achieve adequate control on existing medication
- Improved treatment is especially needed in this medically refractory group
- Development of AEDs with new mechanisms of action provide new avenues for treatment of patients with “refractory” epilepsy
AED mechanisms


Clobazam

- Benzodiazepine, 5-substituted rather than 3-substituted (different affinity for various GABA receptor configurations)
- Designed to produce less somnolence and tolerance than other benzodiazepines

Clobazam efficacy in Lennox-Gastaut syndrome

Ng YT et al. Neurology 2011; 77(15): 1473-81

![Graph showing reduction in weekly "drop" seizures with Clobazam doses]

Clobazam

<table>
<thead>
<tr>
<th>PK properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Bioavailability ≈100 %, $T_{\text{max}}$ 1-3 h</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Protein binding 85 %, $V_d$ 1 L/kg</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP 3A4, 2C19, $t_{1/2}$ 10-30 h</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Decreased dose in patients with renal or hepatic impairment</td>
</tr>
</tbody>
</table>

Clobazam dosing

- Dose range children <30kg, start 5 mg/day, titrate up to 20 mg/day as needed
- Dose range adults 10-40 mg/day as 2 divided doses, available as 5,10,20 mg
- Conservative start: 5 mg hs x 1 week, increase by 5 mg/week to target 20mg/day

Perampanel

- FDA-approved October 23, 2012
- Adjunctive treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy ages 12 years and older
**Perampanel**

<table>
<thead>
<tr>
<th>PK properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Absorption delayed 2 h with food</td>
</tr>
<tr>
<td>≈100%, Tmax 0.5-1.5 h</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Possible displacement interactions with other highly bound AEDs</td>
</tr>
<tr>
<td>Protein binding 96%, Vd 77 L/kg</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Linear relationship between dose and serum concentration</td>
</tr>
<tr>
<td>CYP 3A4, t1/2 70-110 h</td>
<td>Long half-life, steady-state after 14 days</td>
</tr>
<tr>
<td></td>
<td>Induction by CBZ, OXC, PHT, 2-3-fold</td>
</tr>
<tr>
<td>Excretion</td>
<td>Decreased dose in patients with hepatic impairment, renal (not yet investigated)</td>
</tr>
</tbody>
</table>

Bialer et al., Epilepsy Res, 2010

**Perampanel**

- **Non-enzyme-inducing AED regimens:**
  - 2 mg qHS
  - May increase daily dose by 2 mg at weekly intervals based on response and tolerability to 8-12 mg qHS
- **Enzyme-inducing AED regimens (eg, phenytoin, carbamazepine, oxcarbazepine):**
  - 4 mg qHS
  - May increase daily dose by 2 mg at weekly intervals based on response and tolerability to 8-12 mg qHS
Perampanel

• Unique theoretical concerns for perampanel include behavioral and psychiatric side effects because of the drug’s mechanism of action (similar to phencyclidine, or PCP).
• Clinical trials included careful monitoring for psychiatric side effects, including anger; aggression; unfavorable changes in mood, personality or behavior; and other behavioral symptoms, including the emergence of suicidal thoughts or gestures
• Perampanel psychiatric profile overall comparable to placebo


Generic antiepileptic medications

• Most AEDs, both “traditional” and “new,” are available in generic formulations
• Variations in bioavailability of generic preparations of AEDs is a concern
• There are multiple issues in clinical use of generic AEDs.
Carbamazepine

$8.00
09/23/03
USAL.

PROMISED TIME
WED. 2:00 PM
09/24/03

QUANTITY
210

DIRECTIONS
TAKE 1 AND 1/2 TABLETS BY MOUTH EVERY MORNING. TAKE 1 TABLET AT NOON, TAKE 1 AND 1/2 TABLETS IN THE AFTERNOON AND TAKE 2 TABLETS EVERY EVENING.

INGREDIENT NAME:
CARBAMAZEPINE (kar-ba-MAZ-e-pan)

COMMON USES:
This medicine is an anticonvulsant used to treat seizures, determined by your doctor.

HOW TO USE THIS MEDICINE:
Follow the directions for using this medicine provided by your doctor. Do not exceed the dosage prescribed. If you miss a dose, take it as soon as you remember it. If you are not sure what to do, skip the missed dose and go back to your regular dosing schedule.

Carbamazepine

Carbamazepine is a medication used to treat certain types of epilepsy and trigeminal neuralgia. It works by increasing the activity of a chemical in the brain that helps to control seizures. Carbamazepine is available only with your doctor's prescription. It is not known if this medicine is safe to use during pregnancy or if it will harm a nursing baby.

Before using this medicine, tell your doctor if you have any allergies, if you are pregnant, nursing, if you are using any other medications, or if you have certain medical conditions (such as kidney disease, liver disease). Carbamazepine may cause dizziness or lightheadedness, which can increase your risk of falling. Be careful when driving or performing other tasks that require attention and skill. Avoid using alcohol, which can increase your risk of side effects of this medicine. Do not share this medicine with others unless they have the same condition you have. It is illegal and dangerous to share this medicine with others.

Side effects of this medicine may include dizziness, feeling tired, feeling sick, and a skin rash. If you experience severe dizziness, confusion, or difficulty breathing, seek medical attention immediately.

The information provided is for educational purposes only and is not intended to replace professional medical advice, diagnosis, or treatment. Always consult with a licensed healthcare professional before making any changes to your medication regimen. If you have any questions about this medicine, please consult your pharmacist or doctor.

May 2017
The unique Carbamazepine delivery system is made up of 35% immediate-release beads, which release carbamazepine directly into the bloodstream. Carbamazepine is metabolized by the liver, so it is important to avoid using it with other medications that can affect liver function. It is also important to avoid using this medicine with other medications that can affect the kidneys. Always consult with a licensed healthcare professional before making any changes to your medication regimen. If you have any questions about this medicine, please consult your pharmacist or doctor.
AAN position statement on generic medications in epilepsy

• The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval.


FDA equivalence requirements

• The following criteria are necessary for a generic product to be considered equivalent
  – the 90% confidence interval of the log-transformed ratios of AUC
  – Cmax between brand and generic products must fall within the range of 80% to 125%.

**Terminology**

![Graph showing concentration over time with peaks labeled Cmax and Cmin.](image)

**Multiple generic substitution**

- All generic medications are compared to brand name formulation as reference.
- Theoretical variation of Cmax between formulations of generics:
  - Formulation A 125% of reference
  - Formulation B 80% of reference
  - Switching between formulation A and B would result in a 64% decrease in Cmax
Generic substitution of topiramate

- Review of medical and pharmacy claims data to investigate clinical and economic consequences following generic substitution of one vs multiple generics of topiramate
  - 1,105 person-years of brand use, 233 person-years of single-generic use, and 92 person-years of multiple-generic use.
- Medical resource utilization and costs were compared using multivariate regression analysis during periods of “brand,” “generic,” and “multiple generic” use.
- Multiple-generic substitution of topiramate was significantly associated with hospitalizations and injuries

Pharmacokinetic principles

• Drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption
• Predictability of drug absorption is greatest in rapidly dissolving, highly permeable medications
• Different AEDs have more or less favorable dissolution and GI permeability profiles.


Comparing Bioequivalence (BE) of Generic Antiepilepsy Drugs (AEDs)

• Determination of distributions of $AUC_{0-t}$, $C_{\text{max}}$ and their ratios for FDA approved generic AED and reference formulations.
• 258 BE studies evaluated 7156 subjects (male 78%, mean age 32 years).
• In 99% of BE studies, $AUC_{0-t}$ for reference and generic formulations varied by less than 15% (90% CI);

Comparing Bioequivalence (BE) of Generic Antiepilepsy Drugs (AEDs)

• BE studies support most patients switching from reference to generic AED formulations, however, switches between generic AED formulations, particularly those with low solubility should be minimized.

• Generics with low GI permeability (gabapentin) and those with low solubility (oxcarbazepine, carbamazepine, and phenytoin) proved to have the greatest variability in bioequivalence, as defined by Cmax.


EQUIGEN study

• Bioequivalency studies of antiepileptic drugs (EQUIGEN)
• Single dose cross-over design study
• Ongoing study which will give prospective information about pharmacokinetics of generic substitution

Suggestions for generic substitution of AEDs

- Consider pharmacological characteristics of the AED
- Consider if dosage adjustments are reasonable
- Encourage patients to research the cost difference between brand-name medications and generics
- Use the opportunity to counsel patients on compliance/adherence and avoid triggers (alcohol, sleep deprivation)

Titrating and monitoring

- seizure severity
- AED levels
Case 1

• 18 year old woman with a history of a single episode of loss of consciousness, preceded by an unusual epigastric sensation, progressing to a secondarily generalized tonic-clonic seizure
• She presented on a dose of levetiracetam 250 mg twice daily
• She reported intolerable side effects (lethargy) to levetiracetam at higher doses.

Evaluation:
  – EEG showed right temporal epileptiform discharges
  – MRI was normal
• After 6 months of AED therapy on levetiracetam 250 mg twice daily, she had a repeat seizure 3 days after abrupt self-discontinuation of her medication
• After restarting levetiracetam 250 mg twice daily, she has remained seizure free for one year.
Case 2

- Development of complex partial epileptic seizures after an episode of encephalitis at age 7
- Treatment with multiple AEDs, left anterior temporal lobectomy, and vagal nerve stimulator
- Typical seizures with onset of a feeling of nausea and lightheadedness followed by loss of consciousness continue on a weekly basis at age 67

Epileptic seizure severity

- Both patients presented with complex partial seizures, due to temporal lobe epilepsy
- The severity of seizures differed markedly between the two cases
- What are the factors responsible for the differences between the subjects?
Concepts of seizure severity


Therapeutic antiepileptic drug levels

- 84 patients followed prospectively, on monotherapy phenytoin, phenobarbital, and carbamazepine
- All studied patients were seizure free for one year
- AED levels were recorded after patients had their last seizure and following control for one year
- Medications increased until clinical toxicity if necessary

Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: Individual variation in relation to seizure frequency and type. Neurology; 1984;34:1252-5.
Phenytoin therapy

- Author’s experience with over 3000 epileptic patients on phenytoin
- Phenytoin 500 mg daily to start therapy.
- Follow in 4 to 5 days.
  - If toxicity developed, decrease the dose to 400 mg daily.
  - If there was no toxicity, continue 500 mg daily.
  - "Dilantin inebriation" in 14-45% in this series.

Concepts of AED levels in epilepsy

- Epilepsy is a heterogeneous disease process, varying greatly in severity between individuals
- “Low” levels may control mild epilepsy, while “high” levels may not control severe epilepsy
- Due to lack of objective evidence for “therapeutic” level ranges, the FDA did not recommend plasma levels for newer AED agents (those approved since 1993)

Proper use of AED levels

- The primary goals of AED treatment should be control of seizures without medication side effects
- AED levels should be ordered only when there is a clinical indication
- Clinical situations in which medication levels can be helpful
  - compliance issues
  - toxicity
  - uncontrolled seizures
  - concomitant medication changes

Overview of medical treatment of epilepsy

- Treatment should be started with a single drug (monotherapy).
- In general, the strategy is to gradually titrate the dosage to that which is maximally tolerated and/or produces seizure freedom (start low and go slow).
- Treatment should be monitored regularly. At regular office visits, physicians should ask and record seizure frequency and medication side effects.


AED withdrawal

- 1013 subjects seizure free for at least two years
- Randomization to continued AEDs or slow withdrawal, with two year outcomes of seizure freedom at 78% (continued AEDs) and 59% (withdrawal)
- Important factors
  - longer seizure-free periods before attempting drug withdrawal reduced recurrence
  - A history of tonic-clonic seizures treated with more than one AED increased recurrence

Conclusion

• Choosing both “traditional” and “new,” as well as generic medications, should be individualized for each patient
• Titrating and monitoring of AED treatment should incorporate concepts of seizure severity
• Decisions concerning withdrawal of AED therapy should occur with the understanding that AED withdrawal carries a risk of seizure recurrence
Algorithm in Treating Patients with Drug Resistant Epilepsy: Lesional and Nonlesional

John Stern, MD

Clinical Guidelines
Evaluation Algorithm

- History
  - Habitual seizures epileptic?
  - Habitual seizures one type?
  - Non-progressive cerebral disease?
  - Good surgical risk?
  - Drug resistant seizures to appropriate medications at appropriate doses?

Seizure Freedom with Successive Pharmacotherapies

Drug Resistant Epilepsy

- When all existing medical therapy options fail
  - Impossible to determine clinically
- Diagnostic test
  - No surrogate marker exists
- Syndromic diagnosis
  - Classification is still emerging
- Medication response history
  - If first AED failed, 11% became seizure free
  - If two AEDs failed, 3% became seizure free
- International League Against Epilepsy definition
  - Failure of appropriate use of 2 AEDs to produce seizure freedom
  - Response determined after 12 months or 3x seizure interval

Evaluation Algorithm

- History
- Essential diagnostic testing
  - Interictal EEG
    - Focal, bilateral, multifocal, or generalized?
  - Epilepsy protocol MRI
    - Abnormality requiring surgical treatment?
  - Ictal behavior and EEG
    - Complete collection of seizures?
- Supplemental diagnostic testing
  - Neuropsychological testing
    - Focal, bilateral, multifocal, or generalized dysfunction?
  - Functional MRI
    - Co-localization of key function with abnormal region?
  - FD-Glucose PET
    - Focal, bilateral, or multifocal hypometabolism?
Video-EEG Monitoring

Limbic Auras

- Olfactory and Gustatory
- Autonomic
  - Internal Milieu
    - Epigastric
    - Substernal
    - Abdominal
    - Nausea
  - Piloerection
  - Warmth / Chill
  - Urinary urge
- Paramnestic
  - Déjà vu
  - Jamais vu
  - Presque vu
  - Prescience
- Emotional
  - Fear
  - Sadness
  - Elation
  - Spiritual
Neocortical Auras

- Somatosensory
  - Unilateral / Bilateral
  - Painful
- Vestibular
- Visual
  - Unilateral / Bilateral
  - Simple / Complex
  - Familiar / Unfamiliar
- Auditory
  - Unilateral / Bilateral
  - Words / Sounds
  - Familiar / Unfamiliar
- Synesthetic
  - Specific sensory modalities
- Indescribable

Ictal Behavior

- Blinking
  - Unilateral
  - Unilateral with lower face
  - Bilateral
- Automatisms
  - Unilateral / Bilateral
- Turning
  - Version (unnaturally forced & sustained)
    - With or without gaze and facial contraction
    - Deviation (natural in appearance)
- Posturing
  - Tonic / Clonic / Dystonic
  - Unilateral / Bilateral
  - Symmetric / Asymmetric (Fencer's or Figure of 4)
EEG and MRI


PET-MRI Co-registration

Cognitive Testing

• Is cognitive dysfunction present?
  – Is it global, multifocal, lateralized, or focal?
• Is the dysfunction concordant with the putative epileptogenic zone?
• How close is normal function to the putative epileptogenic zone?

Evaluation Algorithm

• History
• Essential diagnostic testing
• Supplemental diagnostic testing
• Assessment of results
  – Does MRI identify focal abnormality that potentially epileptic?
    • Are behavior and EEGs concordant with MRI lesion?
  – Does PET identify focal hypometabolism?
    • Are behavior and EEGs concordant with PET finding?
  – Are MRI and PET concordant?
  – Is neuropsychological testing concordant with EEG, MRI, and PET?
    • If yes, consider tolerability of focal resection
      – Wada test?
    • If no, consider whether additional studies may help
Evaluation Algorithm

- History
- Essential Diagnostic Testing
- Supplemental Diagnostic Testing
- Assessment of results
- Additional testing
  - EEG source analysis
    - Reconsider accuracy of interictal and ictal localizations
  - MEG source analysis
    - Reconsider accuracy of interictal (and ictal) localizations
  - Ictal SPECT
    - Reconsider accuracy of ictal localization

Electroencephalographic Source Analysis
Magnetoencephalographic Source Analysis

Ictal SPECT
Evaluation Algorithm

• History
• Essential Diagnostic Testing
• Supplemental Diagnostic Testing
• Assessment of Results
• Additional Testing
• Does evaluation indicate a specific localization?
  – If yes, what is proximity to eloquent cortex?
  – If no, does it indicate a region?
  – If no, does it indicate two putative localizations?
  – Can intracranial EEG increase certainty of localization and extent?
    • Implantation should be hypothesis driven
    • Technique choice based on coverage needs

Intracranial Techniques

• Depths
  – 3-dimensional lesion
  – Midline target
  – Multi-lobar lesion
  – Poorly localized and non-lesional

• Grids / Strips
  – Surface lesion
  – Adjacent eloquent cortex
  – Localized and non-lesional
Depth Electrodes

Grid and Strip Electrodes
### Surgical Procedures

- **Lesionectomy**
  - Margins determined by imaging findings
- **Cortical Resection**
  - Margins determined by syndrome, function, and dysfunction
- **Hemispherectomy**
  - For diffuse hemispheric pathology
- **Corpus Callosotomy**
  - Disconnection impairs interhemispheric seizure spread
- **Multiple Subpial Transection**
  - Impairs seizure spread while preserving normal function
- **Stereotactic Thermo-ablation**
  - For deep targets
- **Responsive Neuro-stimulation**
  - For two foci or co-localized with eloquent cortex
- **Deep Brain Stimulation (to anterior thalamus)**
  - For poorly localized, multi-focal, or co-localized with eloquent cortex

### Multiple Subpial Transection

- Synchronization of epileptiform activity relies upon horizontally-oriented (tangential) connections
- Normal function relies upon vertically-oriented (perpendicular) column connections

Stereotactic Thermoablation

Responsive Neurostimulation

Conclusion

- Determining candidacy for epilepsy surgery is one of the most complicated undertakings in medicine.
- A structured approach can assure that the evaluation is both comprehensive and systematic.
- Consideration of each test’s value and significance through the evaluation benefits the evaluation’s accuracy.
- *Surgical success depends on the evaluation.*
Algorithm in Treating Seizure Emergencies

Joseph I. Sirven, MD
Professor and Chair
Department of Neurology
Mayo Clinic
Phoenix, Arizona

Case: 39 yo female

- 39 y/o female
  - Hospital employee
  - Presents with a single GTC
  - History of bronchitis for 7 days
    - On unknown antibiotic
  - On gabapentin and “Ultram®” for chronic abdominal pain
Case

- Smoker
- Family with recent upper respiratory infection

- Evaluation in the ER shows the patient
  - Follows simple commands
  - Not back to baseline
  - Unable to converse

Case

- The patient had immediate EEG performed with
- The following EEG was captured...
What is happening and what’s next?

- Lab tests?
- Imaging?
- Antiepileptic Medication?
- Other?

When does a seizure become status?

- Isolated Seizures
- Seizure Clusters
- Status Epilepticus
Definition of SE

- SE is defined as 5 min or more of:
  - (i) continuous clinical and/or electrographic seizure activity or
  - (ii) recurrent seizure activity without recovery (returning to baseline) between seizures.

- This definition was adopted for the following reasons:
  - Most clinical and electrographic seizures last less than 5 min and seizures that last longer often do not stop spontaneously.
  - Animal data suggest that permanent neuronal injury [11] and pharmacoresistance may occur before the traditional definition of 30 min of continuous seizure activity have passed.

Pathophysiology of Convulsive SE

![Pathophysiology Diagram](image)
Diagnostic tests in SE- All Patients

**All Patients**

1. Fingerstick glucose
2. Monitor vital signs.
3. Head computed tomography (CT) scan (appropriate for most cases)
4. Order laboratory test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels.
5. Continuous electroencephalograph (EEG) monitoring

**Consider based on clinical presentation**

- 1. Brain magnetic resonance imaging (MRI)
- 2. Lumbar puncture (LP)
- 3. Comprehensive toxicology panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine)
- 4. Other laboratory tests: liver function tests, serial troponins, type and hold, coagulation studies, arterial blood gas, AED levels, toxicology screen (urine and blood), and inborn errors

AEDs for Status epilepticus

- **Benzodiazepines**
  - Diazepam
  - Lorazepam
  - Midazolam
- **Phenytoin (Fosphenytoin)**
- **Phenobarbital**
- **Valproic acid**
- **Levetiracetam??**
- **Lacosamide??**
Established and Early Refractory SE (30 min-48h)

- Generalised-convulsive (or subtle) SE
  - Intravenous midazolam: 0.2 mg/kg → 0.2-0.6 mg/kg/h and/or
  - Intravenous propofol: 2 mg/kg → 2-30 mg/kg/h
- Focal-complex, myoclonic, or absence SE
  - Further intravenous or oral antiepileptic drug
    - Valproate*, levetiracetam, lacosamide, topiramate, pregabalin, or other

Late refractory SE (>48h)

- Pentobarbital (thiopental): 5 mg/kg (1 mg/kg) → 1-5 mg/kg/h
- Other drugs: Lidocaine, verapamil, magnesium, immunomodulation
- Other anaesthetics: Isoflurane, desflurane, ketamine
- Other approaches: Surgery, VNS, tTMS, ECT, hypothermia, ketogenic diet
Kaplan–Meier Curves Comparing the Durations of Out-of-Hospital Status Epilepticus after Treatment with Prehospital Management of Status Epilepticus Diazepam, or Placebo.

New Delivery systems

**IM dosing- RAMPART**
- IM midazolam vs IV Lorazepam (N= 448)
  - 10 mg Midazolam vs 4 mg IV lorazepam
  - 73.4% vs 63.4%
  - TTT 1.2 min vs 4.8 min
  - TTSC 3.3 min vs. 1.6 min

**Others**
- Diazepam autoinjector
  - Time to next seizure 1.18 hr vs 2.7 hour placebo
  - Rescue 55% placebo vs. 35.4% AI
- 13 products under investigation with a benzo
Primary Outcome According to Treatment Group: Rampart

RAMPART Study: Pre hospital IM Midazolam vs. IV Lorazepam

Diazepam versus Lorazepam  PECARN Trial

- Patients 3 months- 18 years
- 273 patients randomized to 0.2 mg/kg diazepam (n= 140) versus 0.1 mg/kg of lorazepam IV (n= 133)
- Primary measure cessation of status within 10 minutes
- 72.1% diazepam vs. 72.9% lorazepam
- Lorazepam led to more sedation
- No difference
- JAMA 2014
Rate of Successful Initial VA Cooperative Study of Generalized Convulsive Status Epilepticus Each of the Four Regimens.


Treatment: Emergent initial therapy

<table>
<thead>
<tr>
<th>Strong Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High or Moderate Quality Evidence</strong></td>
</tr>
<tr>
<td>• Benzodiazepines should be given as emergent initial therapy</td>
</tr>
<tr>
<td>• Lorazepam is the drug of choice for IV administration</td>
</tr>
<tr>
<td>• Midazolam is the drug of choice for IM administration</td>
</tr>
<tr>
<td>• Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated</td>
</tr>
</tbody>
</table>

Treatment: Urgent control therapy

<table>
<thead>
<tr>
<th>Strong Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High or Moderate Quality Evidence</strong></td>
</tr>
<tr>
<td>• Urgent control AED therapy recommendations include use of IV fosphenytoin/phenytoin, valproate sodium, or levetiracetam</td>
</tr>
</tbody>
</table>

Brophy, et al NCC 2012
The following tests are obtained

- CT and MRI are normal
- WBC elevated at 11,000
- LP performed and negative

Main Points

- Define SE and apply it rigorously to all cases
- Have a definite treatment protocol
- Get EEG early, use frequently and until patient recovers
Case

• The patient has been treated with:
  – 6 mg lorazepam (2mg x 3)
  – fosphenytoin
• Follow-up evaluation
  – Vital signs stable
  – No apparent abnormal movements
  – Still unresponsive
  – The patient had the following EEG obtained...

EEG
Case

• What is happening with the patient?
• What is the next step in treatment?
• Next best choice?
  – Use propofol
  – Use midazolam
  – Use pentobarbital
  – Use inhalational agents

How do you define Refractory SE?

• Time
  – SE persisting longer than 60 minutes
• Failed Meds
  – Another benzodiazepine & an antiepileptic drug
    • Bleck 1993
  – Accounts from 9-31% of SE
  – Very high morbidity/mortality
Refractory SE

• Defined: Patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) are considered refractory.

Case

• The following is done:
  – Use of propofol
  – Use of midazolam
  – Use of pentobarbital
  – Use of inhalational agents

• Day 49 follow-up EEG...
Case Questions

• Is the patient in SE?

• What other therapeutic options are left?

Refractory SE: Which drug?

• Pento vs Propofol vs. MAZ
  – No difference in mortality
  – Pentobarbital has a lower freq of acute treatment failure
  – Hypotension more frequent with pentobarbital

• Claasen 2002
Which AED for SE? Expert Consensus

• Expert consensus for using intravenous lorazepam for the emergent (first-line) therapy of SE in children and adults.
• For urgent (second-line) therapy: phenytoin/fosphenytoin, valproate sodium, and levetiracetam; with variation by the patient age
• Physicians who care for adult patients chose cIV therapy for RSE, especially midazolam and propofol.
• In children, propofol is avoided.
• Pentobarbital was chosen later in the therapy for all ages.

• Neurocritical Care Society Status Epilepticus Guideline Writing Committee  J Neurocritical Care 2012

Main points

• Define refractory SE and be consistent
• Have a consistent SE protocol
Management Issues

• Consider the following management issues
  – Duration of AED drips
  – Titration goal
  – Oral AEDs
  – Serum levels

What Next?

• Ketogenic diet
• Surgery
• Neuromodulation
• Immune based treatments?
Immunopathology and Status Epilepticus

**Anti-Hu (ANNA-1)**
- Lung, Kidney, Breast, Prostate
- Neuropathy, ataxia, cognitive impairment, neuromuscular junction disorder, myelopathy, aphasia

**ANNA-2**
- Cervical, Lung, Bladder, Ovarian
- Brainstem symptoms, spasticity, extrapyramidal, autonomic dysfunction, cognitive impairment

**ANNA-3**
- SCLC, esophagus
- Ataxia, neuropathy, autonomic dysfunction, brainstem symptoms, cognitive impairment, myelopathy

**Anti-Ta**
- Testicular
- Cognitive impairment, ataxia, neuropathy, motor neuron disease

**Anti-Ma**
- Breast, Parotid, Lung, Testicular
- Cognitive impairment, headache, brainstem symptoms, ataxia, extrapyramidal, dyssomnia

**Anti-CRMP5**
- SCLC, Thymoma
- Cognitive impairment, psychosis, extrapyramidal, ataxia, brainstem symptoms, neuropathy, autonomic dysfunction, neuromuscular junction disorder

**Voltage-gated potassium channel (VGKC)**
- SCLC, Thymoma, Breast, Hematologic
- Cognitive impairment, hallucinations, dyssomnia, extrapyramidal, myoclonus, autonomic dysfunction, neuropathy

**N-Methyl-D-Aspartate (NMDA) Receptor**
- Ovarian, Testicular, SCLC
- Psychiatric, extrapyramidal, autonomic dysfunction

**Glutamic Acid Decarboxylase (GAD)-65**
- SCLC, pancreatic, thymoma, diabetes mellitus
- Stiff-person syndrome, ataxia

“Powell Doctrine” for Status Epilepticus

“Patient and Families want everything done assuming it is not a lost cause.”

• **Is there a plausible exit strategy to avoid endless entanglement?**
Can you predict SE Survival?

**STESS score**

- Prior to Treatment
  - Age
  - History of Seizures
  - Seizure Type
  - Extent of Consciousness

- 154 patients
- Excellent negative predictive value (0.97)

Rossetti 2006, 2008
Main points

• Patients can die from treatment and complications
• Prognosis can be difficult to predict early on
• Need to establish how aggressive should we be in pursuing treatment and how long can you continue treatment?