Joint Session with ACOFP and Mayo Clinic

So One of Your Patients has Seizures?

William Tatum IV, DO
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Name of CME Activity: 2015 AOA/ACOFP Osteopathic Medical Conference & Exposition (OMED)

Dates and Location of CME Activity: October 17 - October 24, 2015 Orange County Convention Center Orlando, Florida

Topic: So One of Your Patients Has Seizures.... Monday, October 19, 2015 9:00-10:00am

Name of Speaker/Moderator: William Tatum IV, DO

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<th>Organization With Which Relationship Exists</th>
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OFF-LABEL USE OF ANTI-SEIZURE DRUGS, DEVICES, SURGERY...

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Date: 9/1/2015

Please fax this form to ACOFP at 866-328-1835, or e-mail to joank@acofp.org as soon as possible.
Deadline: Friday, September 11, 2015
So Someone You Know Has Epilepsy?

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Mayo College of Medicine
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Jacksonville, Florida USA

Faculty Disclosure

- **Financial Involvement**
  - National Board Affiliations (Neurophysiology)
    - ABCN, ACNS
  - Consultant/speaker’s bureau/honoraria
    - Demos Publishers, Springer Publishers
  - Research support
    - Brain Sentinel

- **Significant Financial Involvement creating a conflict of interest**
  - None

- **Off label discussion**
  - None
KH is a 24 year old female with a prior Oligodendrogloma presents to the ED after 3 witnessed “grand mal” seizures. She is taking Buspar 10 mg PO TID, Xanax 1 mg PO TID, and Tegretol XR 400 mg PO BID with weekly attacks failing LTG and GBP...

**Epilepsy**

- **Definition:** Epilepsy exists after a single unprovoked seizure when the risk of a recurrence is >60%.¹
  - Nearly 3 million people in U.S (50 million worldwide)
  - One epileptic seizure/life-time occurs in 1/10 people
- **Approximately 70% of adults with new-onset epilepsy have focal seizures.**
- **The cause is unknown in 62%.
  - In the rest, stroke in 9%, trauma 9%, alcohol 6%, neurodegenerative dz 4%, static encephalopathy 3.5%, brain tumor 3%, and infection in 2%.
  - An age-related predisposition exists that reflects cause.

¹. Fazekas R et al. Epilepsia 2002; 43:1:121-135
Seizures are a Symptom

- Brain malformations and infection during childhood
- Trauma and brain tumor in mid-life
- Stroke and dementia in later life

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EEG

- **Sensitivity:** (Low-moderate)
  - First recording is “+” IEDs in 29-55%.
  - Recovery is related to brain location (temporal vs frontal).
  - Increases to 85% with repeated study, sleep deprivation, <24 hrs.
- **Specificity:** (Very high)
  - IEDs are rare in non-epileptic people (1-2%).
  - More common in kids (1.9-3.5%) than adults (0.2-0.5%).
- **Video-EEG:** definitive means of diagnosis, classification, and characterization\(^2\).

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A 58 y/o M awoke with a feeling “everything was spinning” worsened by head movement with concomitant nausea and sweating. No LOC was noted and he was A & O x3.

ED= Vertigo
EEG: Generalized Spike-waves
Told no Driving.
Diagnosis: “Seizure D/O”
Couldn’t get to work.
“Sick” from CBZ

A Treatment Plan

Newly Diagnosed

1st
Monotherapy
2nd
Monotherapy
3rd Mono or Polytherapy

Seizure freedom
No Side effects
Video-EEG Monitoring

ASDs (Polytherapy)
Neurostimulation Ketogenic Diet (children)

No

Seizure reduction
Minimize AED side effects
Optimize quality of life

Drug Resistant


Treatments

- **Medical¹**
  - Seizure reduction
  - SE reduction

- **Non-medical²**
  - Neurostimulation³
  - Ketogenic Diet⁴

The First Seizure as Epilepsy

- ASD treatment renders 65-85% seizure free.¹
- Recurrence greatest in the 1st 2 years (21-45%).
  - Response to the first ASD predicts control.¹
  - + risk factors double the likelihood & tx halves it.
    - Prior brain insult (level A)
    - Epileptiform EEG (level A)
    - Abnormal MRI (level B)
- SE in 7-31% (level B)

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²Webe S et al. NJM 2001;345:311-318.
³Cascino GD. Epilepsia 2008;49(Suppl 9):79-84.
Anti-Seizure Drugs

• None alter the course of the disease process ("AEDs").
• All current ASDs provide symptomatic treatment.
  – Effective in focal seizures 2/3rds of the time.
  – Effective in generalized seizures 80-85% of the time.
  – Response to treatment has been stable over time.
• All ASDs potentially have adverse events and none treat
  the non-seizure symptoms (neurocognitive/psychosocial).
• No ASDs are truly prophylactic for prevention of epilepsy
  (due to trauma, stroke, brain tumor etc.).

Choose the Most Effective ASD

• The mainstay of treatment in >90% of patients.
• Choices
  – Conventional: PB, PHT, CBZ, VPA
  – Newer: LTG, TPM, GBP/PGB, OXC, LEV, ZNS, LCS, RUF,
    CLB, GVG, EZO, PER, ESLI [FBM, TGB]
  – Choice based on seizure type and epilepsy syndrome
    • Focal Epilepsy: Essentially all ASDs
    • Generalized Epilepsy: VPA, LTG, TPM, ETH (absence only)
• Advantages of the newer ASDs include tolerability
  and the advantages of conventional ASDs is cost.

Consider Safety

- Steven-Johnson Syndrome
  - Most of the ASDs
- Aplastic Anemia
  - Carbamazepine, oxcarbazepine, felbamate
- Organ Failure (e.g. hepatic)
  - Valproate, felbamate
- Depression
  - Phenobarbital, perampanel, leviteracetam, zonisamide
- Topiramate, lacosamide
- Nephrolithiasis
  - Topiramate, zonisamide
- Visual loss
  - Vigabatrin, ezogabine
- Weight Loss
  - Felbamate, topiramate, zonisamide
- Weight Gain
  - Gabapentin, pregabalin, perampanel, vigabatrin, valproate
- Teratogenesis
  - All ASDs

Women of Childbearing Potential

- Childbearing potential 12-44 years old
- Contraception
- Pregnancy
- Vitamin supplementation
- Precautions

How Many Drugs Do You See?


Spectrum of Use

<table>
<thead>
<tr>
<th>Focal</th>
<th>Generalized</th>
<th>Focal and Generalized</th>
<th>Spectrum Not Established</th>
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<td>Carbamazepine</td>
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<td>Clozapam</td>
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References:

- Harris WD. Current Treatment Neurology 2013

Slide courtesy of Jacqueline French, MD
Genetic Generalized Epilepsy

- Absence, myoclonic, (clonic)-tonic-clonic
- Genetic influence
- Common in children
- Normal neuroimaging and intelligence
- Treatment responsive
  - ETH for CAE\textsuperscript{1,3}
  - VPA\textsuperscript{1,3} (JAE, JME, GTC)
  - LEV, LTG, TPM, ZNS

Juvenile Myoclonic Epilepsy

- A 21 year old female has been out late at night with her friends in college. She has been active in sports and is a cheerleader at University of Florida. She may have had someone slip something into her drink at the party. She recalls that she felt like she had been struck several times with a lightening bolt and then "blacked out". Her friends later noted that she had a "grand mal seizure" and suggested that she see you.

- What is her diagnosis?

\textsuperscript{1} Nicodemus S et al. Neurology 2005;65(suppl 2): S3-S11.
\textsuperscript{2} Nicodemus S et al. JNRP 2004;51:65-78.
Consider Co-morbidities

- **Mental Health issues**
  - Select: LTG, VPA, OXC, PGB
  - Avoid: PB, TPM, LEV, ZNS, PER

- **Pain**
  - Select: GBP, PGB, TPM, CBZ

- **Eating disorder: avoid drugs that impact weight**
  - Weight gain: VPA, GBP, PGB, CBZ, OXC, EZO
  - Weight loss: TPM, ZNS, FBM

- **Hyponatremia (elderly, on diuretics)**
  - Avoid: CBZ, OXC, ESLI (CBZ derivatives)

- **Cardiovascular risks (e.g. high cholesterol)**
  - Avoid: CBZ, PHT (*inducers)

Encephalopathic Epilepsy

- **Clinical features**
  - Cognitive impairment
  - Refractory seizures
  - Severe EEG abnormalities

- **Seizures**
  - Mixed seizure types
  - Generalized motor
  - Tonic and atonic

- **Refractory to treatment often with recurrent injury**
  - Broad spectrum ASDs
  - Surgical procedures

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- Quality of Life
- Limit ASDs
- Side effect reduction
- Minimize injury
- Limit ED visitation
Lennox-Gastaut Syndrome

- A 28 year old mentally retarded hispanic male experienced episodes of “flinching” at 8 months old. Development had global delay of milestone in development. Seizures occurred multiple times daily and was given a “steroid”. At 2 years old he began to manifest multiple seizure types including “grand mal”, “petit mal”, “dropping”, “falls”, and “jerks”. He has failed 11 ASDs.

- What are his options?
Vagus Nerve Stimulation

- VNS has efficacy equal to new ASDs in RCTs.\(^1\)
- Guideline Subcommittee of the AAN.\(^2\)
  - Recommendation: VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy (Level C).
  - VNS may be considered to have improved efficacy over time (Level C).
- Long Term Effectiveness Trial\(^3\)
  - Improvement in HRQoL compared with BMP.
- VNS reduced cardiac electrical instability.\(^4\)
  - T-wave alternans (biomarker for SUDEP) was reduced.

Focal Epilepsy

- Most common type in adults
  - > 60% of epilepsies
  - Focal seizures with and without impaired consciousness
  - Focal evolving to convulsion
- Due to focal CNS “lesion”
- EEG may clarify seizure classification.
- Treatment
  - *Initial: CBZ, LTG, OXC
  - Alternate: LEV

\(^1\)Kranzler S et al. Epilepsy & Behavior 2006;7:S1-564.

Focal Epilepsy

- A 58 year old female is seen for a seizure disorder. She has HTN, DM, osteoporosis, DJD, and hypercholesterolemia on Coumadin for a PE. She has not had a “grand mal” seizure since she was 19 years old.
- She thinks she is having 1-2 “mini-mal” seizures per month. She is on multiple medications and has been followed by her PCP for 40 years on Dilantin® 400 mg PO daily. She see Neurology adds CBZ 800 mg po qD added but levels are low (PHT=7 ug/dl and CBZ 3.6 ug/dl); seizures increased.
- What do you do?

What About Driving?

- State-specific driving laws exist (3 mos- 1 yr.).
- Epilepsy increases the risk of MVAs (up to 7x).\(^1\)
- Fatalities rare (<0.2%).\(^2\)
- Most patients with epilepsy are controlled with ASDs and drive.

**Drug Induction**

- **Reasons**
  - Non-compliance
  - “Fast metabolizer” (20% of AA for 2C9 drugs).
  - Reciprocal induction: both ASDs together lead to combined reduction in serum concentrations.

- **Solution**
  - Transition to CBZ monotherapy (3A4, 2C9)
  - Substitute a different ASD to PHT (2C9)

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A 24 year old male comes to clinic with his girlfriend. She describes staring spells followed by erratic behavior. The patient denies a problem and states that his girlfriend is making things up to get back at him for getting her pregnant. MRI brain and EEG is normal.

- **Treatment** depends on seizure frequency.
- **In-patient VEM:**
  - 39-49% of seizures were recognized.¹,²
  - 30% of people denied all seizures
  - 23% of people were aware of all their seizures.³
- **Out-patient CAA-EEG:**
  - 62% of seizures were recognized.³
- Left temporal and bitemporal Sz a predictor⁴

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What about Epilepsy and Pregnancy?

- Globally 15 million WWE = child-bearing age.
- Seizures may increase in 25%
  - Uncontrolled GTC Sz can have devastating consequences (> 5 associated with lower IQ).
  - 10-fold increase in SUDEP in pregnant WWE.
- MCM in 4-8%
- VPA impairs cognitive development
  - 6 years post-partum
  - Lower IQ (~ 10 IQ points)
  - Dose-dependence > 800 mg/day

ASDs-Hormonal Contraception

Pregnancy Potential
- Carbamazepine, OXC, Esli
- Phenobarbital
- Phenytoin
- Primidone
- Topiramate*  
- Rufinamide
- Clobazam
- Eslicarbazepine
- Perampanel

Safe
- Divalproex
- Ethosuximide
- Gabapentin
- LamotrigineA
- Levetiracetam
- Zonisamide
- Tiagabine
- Lacosamide
- Vigabatrin
- Ezogabine

* Potential interaction at 200mg/day

A Potential interaction with CYP induction
Prevalence of Major Malformations

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<th>General Population: 1.1%</th>
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<tr>
<td>Drug</td>
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<td>Internal Control</td>
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<td>External Control</td>
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North American Pregnancy Registry Fall 2014

What about Pharmacogenomics?

- Influence on management (e.g. SCN1A, GLUT-1 def, GRIN2A)
- Influence on ASD treatment consequences.
  - Asians are at risk for TEN/SJS on CBZ when found to have a HLA-B 1502* allele.
  - CYP2C genes (10q23.33) associated with PHT-related severe cutaneous reactions.
  - HLA-B 1502* testing recommended in all Asians prior to starting CBZ and OXC.
What’s Next in Line for “AEDs”?

• Treating chronic epilepsy is different than treating developing hyperexcitable networks in animal models.
• Drugs that treat recurrent seizures may be ineffective in preventing the development of a first seizure.
• Trials in patients with brain lesions (e.g. tumors and trauma) do not support the concept of prophylaxis.
• Questions remain whether ASD alternatives (e.g. anti-inflammatory, anti-oxidants, neuroprotectants or inhibitors of neural sprouting can prevent epilepsy.

What About Weed?

• Schizophrenia, illegal, harmful & no evidence for efficacy.
• Activates cannabinoid systems with receptors 1 (G-proteins) & 2 expressed in neocortex and hippocampus.
  – Animal models have shown benefit from cannabidiol (CBD): No controlled trials in humans.
  – Anecdote: Charlotte Figi (Charlotte the Web): Extract high in cannabidiol/low in THC.
• Adverse Events – Early use associated with poor cognitive development and younger psychosis.
  – Synthetic: “Spice” or “K-2” with MS changes, seizures, cardiotoxicity; JW-018 with stroke.
• Drugs – Sativex® approved for spasticity/neuropathic pain in MS/cancer outside USA – 2013 FDA granted orphan drug status of CBD for Dravet syndrome (expanded access).
  – Safety/tolerability open-label trial with Epidiolex (plant liquid CBD extract) in pediatric study.

Co-Authors T.S. Spinal Rep: What’s Neurogics are doing a biomarker.
Drug Resistance
The Reasons

- **Wrong Diagnosis**
  - Psychogenic (physiologic) NEA
  - Bizarre or another seizure type

- **Wrong Drug**
  - for seizure type
  - Drug interactions prevent use

- **Wrong Dose**
  - Too low (ie status)
  - Side-effects limit use

- **Wrong Lifestyle**
  - Poor compliance
  - Inappropriate lifestyle

Confirm the Diagnosis

- A 17 y/o boy grew up in a dysfunctional home environment.
- He had a right craniotomy at 12 years for a parietal lesion (DNET) with subsequent CDH.
- Grand mal seizures began at age 13 years and he failed 5 ASDs.
- He is taking LEV, TPM, KLN and PB when he presents in serial seizures/status epilepticus.

- **What is the next step?**

Kevin P. Leung M. in Therapeutic Strategies in Epilepsy, Freisch J. Delaney N. eds. 2019/100.
Avoid Wrong Drugs

• An 19 y/o male with migraine experienced his first “grand mal” seizure. He was partying the PM before. In the ED he was given IV PHT and maintained on PHT 200 mg po BID (15 ug/dl). He experience an increase in the “dropsies”.
• In follow-up, VPA 250 mg po bid is added to PHT. VPA is increased to 1000 mg po q hs. He complains of dizziness, blurry vision and difficulty walking. Levels are “normal”.
• What is going on?

Inhibitor + Inducer

• Reason
  – VPA and PHT are both highly protein bound ASDs and compete for the carrier protein albumin.
  – PHT free fractions rise (bioactive) with toxicity!
  – The ASD with the higher concentration usually predominate (VPA > PHT).
• Solution
  – Taper PHT
  – Substitute an alternative ASD (e.g. LEV)
A 25 year old male developed jerks at age 12 years. GTC started at 14 years. Diagnosed with JME he remained refractory to ASDs despite VPA, LTG, LEV, and LCS. GTCs were monthly and he presented to clinic with a smartphone video.

Compliance

“Drugs don’t work if you don’t take them.”

C. Everett Koop

Compliance

- Non-compliance is common.
- 37% reported changing their behavior because of SUDEP disclosure.
  - Included improved adherence to medication
  - Potentially mitigating risk of SUDEP.
- Most participants did not report long-term anxiety following disclosure.

http://www.epilepsycouncil.org.uk
Drug-Resistance

- **Surgery Candidates**
  - Disabled by seizures*
  - Drug-resistant
  - Localized/surgically accessible.
  - Healthy/motivated for surgery.

- **Selection**
  - Surgical techniques vary among centers.
  - Patient selection and evaluations varies over time.

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Phase 1 Evaluation

- **Structural (pathology)**
  - **Brain MRI**
    - High resolution
    - Epilepsy protocol

- **Functional (physiology)**
  - **EEG (neuron)**
    - MEG (neuron)
    - Tractography (axons)
    - PET (metabolism)
    - MRS (neurochemistry)
    - SPECT/SISCOM (rCBF)
    - fMRI (vascular)
    - Neuropsychological testing/Wada (function)

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Phase 2 Evaluation

Minimally Invasive Surgery

- 2-5 treatments/patients (mean= 3) in mean of 9.6 minutes (+/- 6.4).
- Workstation thermometry monitors target/collateral tissue.
- Rapid irreversible brain ablation at 60 C (range 40-90 C) with localized heating of tissue with sharp boundaries.
- Optical fibers and laser energy are MR compatible to enable real-time feedback control of laser and tissue ablation.
Intracranial RNS for DRLRE

- Delivers stimulation in response to seizures.
- 18 years old
- 1-2 epileptogenic foci
- Drug-resistant
- Frequent disabling seizures

Quality Indicators in Epilepsy

1. Seizure frequency and seizure intervention specified each encounter.
2. Etiology, seizure type and epilepsy syndrome specified each visit.
3. Ask about side-effects to ASDs each visit.
5. Screen for psychiatric health each visit.
6. Counsel women of childbearing yearly.
7. Refer drug-resistant patients to a CEC q 2 years.
Conclusions

- The treatment of epilepsy requires a definitive diagnosis and classification of seizure/epilepsy type.
- Management is individualized and a shift toward the new ASDs has been based upon Pks and tolerability.
- Drug-resistance is a real problem and non-medical therapies should be considered as a standard of care.
- The future promises better diagnosis and treatment for patients with epilepsy.

Thankyou
tatum.william@mayo.edu