UNDERSTANDING and MANAGING SEIZURES

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Cleveland Clinic
ABTA- Chicago 2013
• To the patients, families and friends, I say thank you for your time today

• Today is about advocating for yourself and your loved one

• A chance to think about options, risks and benefits

• To gain a better understanding about why things are done

• To meet others who share common concerns
Take Home Points

• Brain tumors are uncommon but seizures are common
• The AAN does not advocate AED prophylaxis
• Not everything that shakes is a seizure
• There are many AED drugs available that allow you to tailor the medications best for you
• Sz precautions should be discussed with your doctor including driving
• Many patients will still have sz on the first medication- explore the options including surgery
• Take your medication as rx and talk to your physician about any concerns
Disclosures

• Consultant: UCB

• Investigational drugs will be discussed

• Off-label use of drugs will be discussed
I would like to thank Mary Murphy and Barb Savage - I hope you had a chance to drop around and see our booth and learn a little more about what we can offer

The Rose Ella Burkhardt Neuro-oncology Center at the Cleveland Clinic- multidisciplinary group of specialists

Thanks to the ABTA for what you do everyday
Difference between medical neuro-oncologist and surgical neuro-oncologist?
Seizure Types

- **Generalized** (entire brain) or **partial** (focal) (part of brain)
- **Simple** (no alteration of consciousness) or **complex** (alteration of consciousness)
- Partial sz may generalize
- Events are usually **stereotypical** (the same) and recurrent
- Area of the brain defines the type of symptom
Seizure Type

• Not everything that shakes is a seizure
• Syncope, twitches, pseudoseizures
• Hx provides the best answer for most patients w/o the need for EEGs
• EEG can be helpful when questions about “events” are raised
Canada's Finest
SEIZURES OVERALL IMPACT

• Seizures affect Quality of Life
  – Increased morbidity
  – Decreased independence
  – Depression
  – Anxiety
  – Affects ADL’s i.e. driving, employment, recreation and creates social isolation
  – Plus patients have a TUMOR
SEIZURES & BRAIN TUMORS

• Leads to early diagnosis
• Helps determine location of tumor
• Gray matter more than white matter
• Supratentorial: Parietal, temporal, frontal
• Close to central sulcus
• Rare in infratentorial tumors
LOCATION OF CENTRAL SULCUS
LOCALIZING SEIZURES

Areas of the brain from which partial focal seizures arise.

- Tonic Postural Movement
- Head and Body Turning
- Forced Thinking
- Automatisms
- Olfactory Hallucinations (smell)
- Auditory Hallucinations (hearing)
- Seizures Involving Speech
- Gastrointestinal Sensations
- Salivation
- Mouth
- Tongue
- Lips
- Hand
- Arm
- Leg
- Motor Sensory
- Distortion of Body Image
- Visual Hallucinations (seeing)
- Speech

Automatisms (psychomotor seizures)
Case Example

- 36 y/o RHM to OPD for tx options
- May 06 problems expressing himself
- June/July inappropriate behavior
- MVA 7 12 2006 (probable complex partial seizure (CPS))
- Next wk R hand tingling, expressive problems
- CT/MRI LF mass
- s/p STR 7 17 2006
- Pathology: anaplastic astrocytoma
- Steroids DC 3 days post op
- On PHT for probable sz
CT Brain w/o preop

Large LF mass
L-R shift
Vasogenic edema
Compression LF horn
AEDs: phenytoin

- #1 Rx AED in US
- Generic vs. brand name dosing
- Understand the kinetics MM- nonlinear
- Monitor free vs. bound
- Comfort and IV formulation
Phenytoin

- 1998 FDA approved generic PHT capsule (Parke-Davis)
- State Minnesota: B to G switch w/o physician notification
- 8 patients w increased sz after conversion to generic PHT
- Mean reduction of 13% in bioavailability to brand name
- xPHT brand name: 17.7mg/L vs. 12.5mg/L w generic

Burkhardt et al Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2004;63:1494-1496
Decadron

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder

- Cortisone, 25
- Hydrocortisone, 20
- Prednisolone, 5
- Prednisone, 5
- Dexamethasone, 0.75
- Methylprednisolone, 4
Steroid Interactions

- Decadron is a CYP3A4 inducer- meaning it affects how drugs are broken down in the liver (i.e.: could affect other drugs that you take-like your seizure medication)
Steroids

• Recommend H2 blocker

• AM loading

• Constant re-evaluation
Seizures and Brain Tumors

• ~200,000 Metastases dx per year

• ~60,000 Primary tumors dx per year

• ~20-40% seizure prior to or after initial dx (depends on tumor type and grade and risk could be 80% or more)

• Should everyone go on antiseizure medication?
MR. JACK
Practice Parameter from the AAN


Prophylactic AEDs

• There is little argument about using AEDs once a seizure has occurred and future seizures are predictable

• Our focus here is on prevention of the first seizure
Prophylactic AEDs

• **Why prevent an initial seizure?:**
  - it may occur at a time during the course of the disease process when it will constitute a severe hazard to the patient
  - permanent structural changes forming an epileptic focus may result from repetitive stimulation (**kindling**), preventing early seizures may reduce the risk of establishing a seizure focus
Prophylactic AEDs

- It has been reported that seizure frequency is inversely related to the degree of malignancy
  - oligodendrogliomas 81%
  - astrocytomas 66%
  - ependymomas 50%
  - GBM 42%

AED SE

• Ineffective chemotherapy may be secondary to subtherapeutic drug concn.

Drug delivery to the CNS
How much drug gets there?

Enzyme Inducing Antiseizure Drugs and the Hepatic P450 System

Liver

Rx po or iv

Blood Brain Barrier

Rx reaching brain tumor

Courtesy Skip Grossman
How much drug gets there?

Enzyme Inducing Antiseizure Drugs and the Hepatic P450 System

Liver

Rx po or iv

Blood Brain Barrier

Rx reaching brain tumor

American Brain Tumor Association

Courtesy Skip Grossman
Drug metabolism

• Major route: liver

• Many meds affect the metabolism of chemotherapy drugs by the liver
  – Faster – i.e., meds that induce liver enzymes. Example: phenytoin (Dilantin™)
  – Slower – valproic acid (Depakote™); large quantities of grapefruit juice
  – Not at all – levatirectam (Keppra™)

Anticonvulsants can have major impact on chemotherapy metabolism
How much drug gets there?

Enzyme Inducing Antiseizure Drugs and the Hepatic P450 System

Liver

Blood Brain Barrier

Rx reaching brain tumor

Rx po or iv
Blood-brain barrier

- Protects brain from toxins
- Selection of drugs – they need to get there
  - lipid soluble
    - BCNU, CCNU
  - small molecules
    - cisplatin
    - hydroxyurea
    - procarbazine
    - temozolomide
- Other issues
  - Protein binding
  - Efflux pumps
  - Tumor interstitial pressure
Paclitaxel

- Prototype taxane
- Inhibits tubular assembly
- Inhibits glioma cells in culture
- Used to treat systemic malignancies
- NABTT trial of preirradiation paclitaxel
- Phase II dose 140mg/m² in 10 GBM patients
- 96 hour continuous infusion
- No CR/PR
- No hematologic or nonhematologic toxicity
- 140mg/m² dose was the MTD for systemic malignancies

Paclitaxel

• Steady-state concentrations were **30% lower** than same dose used for systemic cancer
• All patients were on phenytoin- **cyt-P450 inducer**
• Paclitaxel metabolized by cyt-P450
• Revised Phase I dose escalation trial
Paclitaxel

• Phase I: determine MTD for patients on paclitaxel for EIAED and NEIAED
• Phase II for activity at MTD in GBMs
• MTD NEIARD was $140\text{mg/m}^2$
• MTD1 PR only

Prob not effective drug for PBT but have to do trials correctly
Temozolomide

• Does not require metabolism by hepatic mechanisms

• Spontaneously hydrolyzes to active intermediates

• Serum levels and effectiveness should not be altered by co-administration of EIAED
# Anticonvulsants

## Group A
**Anticonvulsants That Induce Hepatic Enzymes**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Dilantin</td>
</tr>
<tr>
<td>Carbamazapine</td>
<td>Tegretol</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Primidone</td>
<td>Mysoline</td>
</tr>
<tr>
<td>Oxcarbazapine (1999)</td>
<td>Trileptal</td>
</tr>
</tbody>
</table>

## Group B
**Anticonvulsants That Cause Modest or No Hepatic Induction**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Depakote</td>
</tr>
<tr>
<td>Gabapentin (1993)</td>
<td>Neurontin</td>
</tr>
<tr>
<td>Felbamate (1993)</td>
<td>Felbatol</td>
</tr>
<tr>
<td>Lamotrigine (1994)</td>
<td>Lamictal</td>
</tr>
<tr>
<td>Topiramate (1996)</td>
<td>Topamax</td>
</tr>
<tr>
<td>Tiagabine (1997)</td>
<td>Gabtril</td>
</tr>
<tr>
<td>Levetiracetam (1999)</td>
<td>Keppra</td>
</tr>
<tr>
<td>Zonisamide (2000)</td>
<td>Zonagram</td>
</tr>
<tr>
<td>Pregabalin (2005)</td>
<td>Lyrica</td>
</tr>
<tr>
<td>Lacosamide (2008)</td>
<td>Vimpat</td>
</tr>
</tbody>
</table>
Results of Rhode Island Study

• 55% of physicians routinely Rx prophylactic AED in newly dx BT patient

• Most Neurosurgeons did (17/21 - 81%)
Study Classification

- **Class I**: evidence provided by one or more well designed randomized, controlled clinical trials, including overviews (meta-analysis) of such trials

- **Class II**: evidence provided by one or more well designed observational studies with concurrent controls such as case-control or cohort studies
• Calculated **odds ratios** were used:

probability of an event (sz on AED)                                      = 1
reference group (sz no AED)
Meta-analysis was conducted on sz incidence using all identified prospective, randomized clinical trials

12 studies met criteria for AED prophylaxis in BT patients (i.e., Prophylactic AED vs. no AED)

4 studies provided Class I evidence
# Meta-analysis of Sz Incidence for Class I Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sz incidence</th>
<th>Sz-free surv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Forsyth</td>
<td>0.82 (0.33-2.01)</td>
<td>1.17 (0.75-1.82)</td>
</tr>
<tr>
<td>Glantz</td>
<td>1.69 (0.61-4.63)</td>
<td>0.88 (0.54-1.46)</td>
</tr>
<tr>
<td>Franceschetti</td>
<td>0.36 (0.07-1.17)</td>
<td>NA</td>
</tr>
<tr>
<td>North</td>
<td>1.85 (0.56-6.12)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td><strong>1.09 (0.63-1.89)</strong></td>
<td><strong>1.03 (0.74-1.44)</strong></td>
</tr>
</tbody>
</table>

**OR**: odds of a sz in the AED prophylaxis gp relative to the no prophylaxis gp
Recommendations

• In patients with newly dx brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors (standard)
Recommendation II

- In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing side effects (guideline)
Summary Cont’d

• AAN does not recommend AED prophylaxis for brain tumor patients
• Think of brain tumors as a chronic disease
• Minimize drug interaction by selecting the AED best for your patient
SEIZURES & BRAIN TUMORS

• High grade tumors 30%
• Due to secondary causes
  – Edema
  – Scar tissue/Surgical changes
  – Progression
  – Treatment effect-irritates brain
• 50% will fail a first line anticonvulsant
• Monotherapy preferred
• 70% recurrence rate if taken off medications after seizure free interval
SEIZURES & BRAIN TUMORS

• Patients with low grade tumors have a higher incidence of seizures but a longer life span
CHOOSING AN ANTICONVULSANT

• Urgency
• IV formulation
• Quick onset
  – Had to rely on 1\textsuperscript{st} generation drugs
  – Now have 2\textsuperscript{nd} generation options
MEDICATION SIDE EFFECTS

Brain Tumor Association®
CHOOSING AN ANTICONVULSANT

- **Initial**
  - Dilantin - Not good for long term
  - Keppra

- **Add on or change**
  - Second generation have less side effects
  - Secondary benefits
DRUG INTERACTIONS

• Interaction with other medications
  – Steroids
  – Chemotherapy
  – Antidepressants
  – Anti-smoking agents
  – Stimulants (fatigue)
DRUG INTERACTIONS

• Interaction with other medications
  – Birth control pills
  – Anticoagulants (DVT’s)
  – Alternative therapies: (70% not reported, potentially epileptogenic)
I'd like this prescription filled.

Sorry, my friend... can't do it.

Why not?

This drug has so many side effects, you're better off with the disease.
American Academy of Neurology

• What are physicians doing since the AAN Guidelines came out?

• Study in 2005 showed **70% of HCP’s not following guidelines** (Soimian, Angelov, Li, 2005, Journal of Neuro-Oncology 74 (2))
PHENYTOIN (DILANTIN)

• Pros
  – IV, quick onset, “old standby”

• Cons
  – fatigue, cognitive impairment, ataxia, visual disturbance, nystagmus, skin reaction
  – Gum changes, bone loss
  – Interactions, fluctuating levels
Carbamazepine (Tegretol)

• **Cons**
  – Similar to dilantin
  – Skin reactions (cross-reactivity)
  – Can affect blood counts (agranulocytosis)
  – Trileptal: hyponatremia

• **Pros**
  – Relieves nerve pain
Valproic Acid (Depakote)

• **Cons**
  – Hepatic clearance
  – Weight gain, hair loss/thinning, increased bleeding time, thrombocytopenia, tremor

• **Pros**
  – Mood stabilizer
  – Headaches
  – In gliomas does it improve tumor tx?
Gabapentin (Neurontin)  
Pregabalin (Lyrica)

• Cons
  – Not good as monotherapy
  – Weight gain, fluid retention

• Pros
  – Relieves nerve pain
B.C. by johnny hart

H ave you put on weight?

N ah, not really. I'm just retaining water.

P lanning to hike the Sahara?
Lamotrigine (Lamictal)

• **Cons**
  – Rash
  – Very slow dose escalation (8 weeks)

• **Pros**
  – Mood stabilizer
Topiramate (Topamax)

• Cons
  – Cognitive impairment “dopamax”
  – Very slow dose escalation
  – Kidney stones
  – Parasthesias

• Pros
  – Weight loss
  – Headaches
Zonisamide (Zonegran)

• Cons
  – Sulfa allergy
  – Rash
  – Kidney stones

• Pros
  – Headache
  – Weight loss
Keppra (Levetiracetam)

- **Cons**
  - Psychological effects: irritability, anger, “Kepprage”
  - Vitamin B6
  - Decrease dose
  - Change therapy
Keppra (Levetiracetam)

• Pros
  – Monotherapy
  – Quick start (days)
  – IV form
  – XR once a day dosing (compliance & side effects)
  – Clinical trials in brain tumor
  – 80% seizure free
  – 73% as monotherapy
Lacosamide (Vimpat)

- **Cons**
  - Partial seizures only as add on
  - Relatively new
  - Dizziness, ataxia, syncope, visual disturbance, increased PR interval
Brain Tumors and Seizures

• Limited research especially in second generation drugs
• Need for more clinical trials of anticonvulsants in the brain tumor patient population
• Combo of chemo and anticonvulsant therapy (helping or hurting?)
Approaches To Seizures

• Patients with intractable seizures
• Undergo Epilepsy evaluation
• Surgery: reduction/elimination of seizures?
Case Study #1

- MD 49 year old R handed female
  - 1st seizure at age 15, partial complex, Dilantin
  - 1st generalized seizure at age 16
  - Phenobarbital, Dilantin, Tegretol, Lamictal, Topamax, Neurontin, Depakote, Primadone, Ativan (w addiction)
  - Longest seizure free period: 2 months
  - Prior neuroimaging negative
  - Required psychiatric intervention
Case Study #1

• Associated with menses so came to CCF to see Epilepsy doctor who specialized in hormone-induced seizures November 2004 (age 43)
• Underwent extensive evaluation in EMU
• Switched to Keppra & Trileptal
• MRI showed left temporal lesion
• Underwent seizure surgery 11/24/04
• Final pathology: **Low grade oligoastrocytoma, 1p intact**
Case Study #1

- Referred to Brain Tumor Center
- Weaned off Trileptal
- Weaned off Keppra late 2008
- Remains seizure free
- Serial scans stable with no further treatment
- Significant improvement in quality of life: driving, working, says she feels like she spent most of her early life “in a fog”
Recent MRI June 2013
Case Study #2

• CP 55 year old R handed female
• 1st seizure at age 24, partial complex
• Associated with menses, intractable (20+/month)
• L temporal lesion resected 3/88: gliosis
• Remained intractable on Tegretol & Topamax
Case Study #2

- Came to CCF 1997 for seizure work up (age 42)
- Extensive work up, EMU
- MRI showed L temporal lesion
- Seizure surgery 3/12/98
- Final pathology: Low grade oligoastrocytoma
Pre-op MRI 1996
Case Study #2

• Referred to Brain Tumor Center
• Seizure free since surgery
• Remains on Tegretol XR 400mg bid by choice
• Serial scans stable without treatment
Recent MRI
New Approach for Intractable Seizures

• Patients with low grade brain tumor (could also be for high grade)
• In remission with good prognosis
• Intractable seizures
• Epilepsy evaluation
• Possible reduction in seizures
• Medication change or surgery
CONCLUSION

• Seizures can significantly impact QOL in brain tumor patients

• Patients with low grade tumors have the highest incidence of seizures but the better prognosis

• In those patients with intractable seizures and in tumor remission, evaluation for Seizure surgery may be a reasonable option
THANK YOU

Any Questions?

2013 Patient and Family Conference
Living with a Brain Tumor: A Holistic Approach
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