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Treatment Options for Seizures: Practical Points in Epilepsy Management

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Treatment Options for Seizures

Practical Points in Epilepsy Management

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CASE ONE

- 21yo male with no significant medical history, has a GTC seizure at 9AM in the presence of two fraternity brothers
- Lasting 2 minutes
- He remained sleepy and confused for 30 minutes, then returned to baseline
- Normal neurological and general exam, except for an abrasion of the right side of the tongue
- CBC, CMP, Tox screen, EKG are normal
THE FIRST UNPROVOKED SEIZURE

- To treat or not to treat?
THE FIRST UNPROVOKED SEIZURE

- Approximately 10% of the population will have at least one seizure at some point in their life.
- Half of these will occur during childhood and adolescence.
- The highest risk is before age 1.
- The higher prevalence of unprovoked seizures is in patients younger than 1 year and older than 65 years.
RECURRENCE RISK
FIRST study

Untreated subjects
- 18% at 3 months
- 28% at 6 months
- 41% at 12 months
- 51% at 24 months

Neurology 1993; 43; 478-483
RECURRENCE RISK
MESS study

- 722 treated / 721 deferred
- Untreated arm recurrence risk
  - 6 months 26%
  - 2 years 39%
  - 5 years 51%
  - 8 years 52%

PREDICTORS OF A FIRST SEIZURE RECURRENCE

- The risk of a recurrence is highest during the period immediately after initial seizure.
- There is no algorithm to predict with absolute certainty who will or will not have a recurrence and when that recurrence will occur.
- What can be summarized today is very much the same as reported in reviews of this same topic written over 10 years ago.
The observational studies taken as a whole, provide an estimate of the 2 year recurrence risk in the range of 40%.

The majority of recurrence occur early with approximately 50% within 6 months of the initial seizure.

Studies with prolonged follow up periods show that 80-90% of individuals who recur do so within 2 years of the initial seizure.
PREDICTORS OF A FIRST SEIZURE RECURRENCE

Consistently associated with an increased risk of recurrence in both children and adults:

1. Abnormal EEG (Epileptiform abnormality)
2. Symptomatic cause or abnormal neurological exam
The diagnostic yield of EEG in the presence of a first seizure is substantial.  
50% of the patients on average have abnormal tracings.  
An EEG done in the first 24 hours after a seizure has a greater probability of detecting epileptiform abnormalities.
CASE ONE

- Normal neurological exam
- Normal EEG
- Normal MRI brain
- No risk factors by history
- NOT TO TREAT

When to treat

- Patient preference
- Two years
- Repeat studies
CASE ONE 1B

- Positive Babinski sign on the right
- Normal MRI brain
- No risk factors
- Drives a Forklift
- No driving for 6 months
- No treatment
- Recurred exactly at 6 months
CASE 2

- 15 year old female
- With recurrent episodes of unresponsiveness
- Staring straight ahead
- Associated with lip smacking
- Lasting 2-5 minutes
CASE 2

- Partial seizures
- Abnormal MRI
- ? Febrile seizures as a child
MESIAL TEMPORAL SCLEROSIS
WOMENS TREATMENT RELATED ISSUES
MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY

- Management of women with epilepsy has specific challenges
- Hormonal influence on seizures
- Interaction of AEDs with contraceptives
- Effect of AEDs on bone health
MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY

- Potentially 1 million WWE of childbearing age in USA
- 3-5 births per thousand will be to WWE
- Issues in women w/ epilepsy who take AEDs during their reproductive years are numerous and complex
MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY

Improve:

- Family planning
- Seizure management
- Pregnancy outcomes
- Patient satisfaction
CATAMENIAL SEIZURES
CATAMENIAL SEIZURES

- Lacks a standard definition
- Reported to occur in 10-70% of women at risk
- Estrogens inhibits GABA mediated inhibition and potentiates glutamate mediated excitation
- Resulting in heightened excitability
- Increased interictal spikes and seizures
CATAMENIAL SEIZURES

- Progesterone opposite effect
- Potentiates barbiturate like ligands at the GABA channel
- Reducing interictal epileptiform discharges
- Fewer seizures
CATAMENIAL SEIZURES

- During the follicular phase (first half of menstrual cycle) estrogen predominates
- Second phase of the cycle Progesterone predominates

Image(s) have been omitted
CATAMENIAL SEIZURES

- During ovulatory cycles most seizures occur approx. 3 days before onset of menses.
- Persists for about 6 days.
- These seizures appear to be triggered by progesterone withdrawal.
- Seizures may also occur at ovulation, precipitated by estrogen surge.
CATAMENIAL SEIZURES

- In anovulatory cycles seizures are more frequent and dispersed = estrogen remains high and progesterone low
- 10% of menstrual cycles in healthy women are anovulatory
- 35% are anovulatory in women with temporal lobe epilepsy
CATAMENIAL SEIZURES

- Chart menses along w/ seizures for at least 4 months
- A day 22 progesterone level (day 1 is the onset of bleeding) < 5ng/mL indicates inadequate luteal phase
- Distinct pattern ≡ Catamenial seizures ≡ different treatment strategies ≡ improved control
CATAMENIAL SEIZURES

Management

- First line treatment: **The most effective AED monotherapy**
- Supplemental daily dose of maintenance AED at the time of expected seizure exacerbation
- 2-3 days before the expected cluster
- Continue for 2 days after the usual cluster duration
CATAMENIAL SEIZURES
Management

- Diamox (off label) 250-1000 mgs in two divided doses
- Tolerance = Intermittent therapy
- 10-14 days around the time of seizure vulnerability
- Should not be used in pregnant women
CATAMENIAL SEIZURES

- Any treatment with hormonal manipulation should be done in collaboration w/ a GYN
- Oral synthetic Progestins not helpful
- Parenteral medroxyprogesterone (Depo-Provera) given in large enough doses to cause amenorrhea = reduction in seizure frequency in some women
CATAMENIAL SEIZURES

- Natural Progesterone (extract of soy in suppository and Lozenge form) over the initial luteal phase of the cycle 100-200 mgs TID or QID
- Prometrium 100 mg capsules
- Progesterone topical cream
- Avoided in anticipation of a pregnancy and in the absence of contraception
CATAMENIAL SEIZURES

- **Antiestrogens: Clomiphene**
- **Reported to reduce seizures in women with intractable partial epilepsy**
- **Side effects:**
  - Hot flashes
  - Polycystic ovaries
  - Unplanned pregnancy
  - Breast tenderness
  - Ovarian overstimulation syndrome
CATAMENIAL SEIZURES

- Women with catamenial seizure pattern may experience improved seizure control after menopause.
- During perimenopause = Irregular Cycles = Fluctuation in gonadal steroids = Worsened seizure frequency.
- Postmenopausal estrogen replacement may exacerbate seizures in some WWE.
CONTRACEPTION
CONTRACEPTION

- Taken in combination with hepatic cytochrome p450 enzyme inducing AED can be ineffective
- 6% per year failure rate of oral contraceptives in women taking hepatic enzyme inducing AEDs
CONTRACEPTION

- Standard prescribed oral contraceptives contain only minimal dosage of hormones
- Even small increases in metabolism lead to contraceptive failure
CONTRACEPTION

- **Levonorgestral** (Norplant; progestin only formulation) implants not a good alternative if using enzyme inducing AEDs, efficacy is reduced.

- **IM medroxyprogesterone** (Depo Provera) higher dosages of progestin has not yet been evaluated for effectiveness in WWE
CONTRACEPTION

- The effectiveness of hormonal contraception in the context of enzyme inducing AEDs remains at approximately the same level as that of IUDs and is superior to barrier methods of birth control.
- Formulations containing at least 50ug of estradiol or mestranol are more protective.
CONTRACEPTION

**INTERACT**
- Phenobarbital
- Phenytoin
- Primidone
- Carbamazepine
- Oxcarbazepine
- Topiramate
- Rufinamide
- Felbamate

**DO NOT INTERACT**
- Valproic Acid
- Gabapentin
- **Lamotrigine**
- Tiagabine
- Zonisamide
- Levetiracetam
- Lacosamide
- Pregabalin
- Vigabatrin
- Ezogabine
AEDs USE IN PREGNANCY
AEDs USE IN PREGNANCY

- 20,000 WWE become pregnant each year
- Seizure frequency may change during pregnancy
- 35% experience increase in seizure frequency
- 55% have no change
- 10% decrease in seizure frequency
AEDs USE IN PREGNANCY

- AED concentrations may change during pregnancy
- Decreased gastric tone and motility
- Increase plasma volume
- Increase in renal clearance
- Albumin levels and protein binding decline
  = Increase in free level
AEDs USE IN PREGNANCY

- AED most appropriate for seizure type and the drug producing optimal control with least side effects remains the AED of choice for WWE
- AEDs are human teratogens
- A specific syndromes are no longer accepted
- Fetal AED syndrome is more appropriate
AEDs USE IN PREGNANCY

- 90% of children born from women with epilepsy will be normal
- Fertility rate 25-33% lower than average
- There is no risk-free anticonvulsant
- Major malformations occur in 2-3% of all live born children
- 4-8% for women with epilepsy on one seizure medication
AEDs USE IN PREGNANCY

Minor congenital malformations

- Facial dysmorphism
- Digital anomalies
- 6-20% infants exposed to AEDs
- Two-fold increase over the general population
- Subtle and outgrown
AEDs USE IN PREGNANCY

Major malformations

- Cleft lip and palate
- Cardiac defects
- Urogenital defects
- 4-6% of infants born to mother w/ epilepsy and taking older AEDs
- 2-4% general population
AEDs USE IN PREGNANCY

- Multiple AEDs at higher risk for congenital malformations and developmental delay
- Higher mean AED concentrations associated with increased malformation risk
- If WWE have been free of seizures on an AED for a period of time, discussion regarding medication withdrawal should be undertaken
AEDs USE IN PREGNANCY

Discontinuation of AEDs may be considered:

- Patient seizure free 2-5 years
- Single type of seizure
- Normal neurological examination and IQ
- EEG normalized with treatment
AEDs USE IN PREGNANCY

- Risk for seizure recurrence is cumulative but greatest in the first 6 months after discontinuing AEDs.
- It is desirable, therefore, that AED withdrawal be completed at least 6 months before planned conception.
A planned pregnancy would be ideal
Major risk of malformation is within the first trimester
No changes to be made after that unless optimization of the regimen is necessary
AEDs USE IN PREGNANCY

- Optimize AED before pregnancy
- Counseling about compliance
- Monitoring non-protein-bound AED levels
- Seizures well controlled with monotherapy ⇒ no change
- Changes in AEDs during pregnancy to reduce teratogenicity is contraindicated
AEDs USE IN PREGNANCY

- MD usually involved after few weeks of pregnancy
- At that point limited advantage to change
- Overlapping AEDs during change exposes the fetus to the effect of an additional AED
AEDs USE IN PREGNANCY

- No consensus for frequency of AED monitoring
- Total AEDs levels fall throughout pregnancy
- Free (non protein bound) level remain constant
- Baseline preconception free level
- Repeat at the beginning of each trimester and last 4 weeks of pregnancy
- AED change or dosage remains clinical based on seizure occurrence or adverse effects
AEDs USE IN PREGNANCY

- Risk for poor pregnancy outcome with optimal care is not a contraindication for pregnancy
- Over 90% will have a good pregnancy outcome
- A minority will have worsening of seizure control during pregnancy
Probable WWE taking AEDs no substantial increased risk for Cesarean delivery (moderate?)

No increased risk of premature contractions/labor/delivery

But increased for WWE who smoke
If seizure free 9-12 months prior pregnancy 84-92% are going to be seizure free
CASE 2

- 15 year old female
- With recurrent episodes of unresponsiveness
- Staring straight ahead
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- Lasting 2-5 minutes
- Partial seizures
- MRI Mesial Temporal Sclerosis
- ? Febrile seizures as a child
AED CHOICE

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- Phenobarbital
- Phenytoin
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- Carbamazepine
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- Topiramate
- Rufinamide
- Felbamate

DO NOT INTERACT

- Valproic Acid
- Gabapentin
- Lamotrigine
- Tiagabine
- Zonisamide
- Levetiracetam
- Lacosamide
- Pregabalin
- Vigabatrin
- Ezogabine
FOLIC ACID SUPPLEMENTATION

- PHE, CBZ, and barbiturates can impair folate absorption
- Pre-pregnancy and early pregnancy supplementation with folic acid for WWE during reproductive years is recommended
- Folic acid supplementation reduces primary and secondary risk for neural tube defects in infants of women who do not take AEDs
FOLIC ACID SUPPLEMENTATION

- Optimal dose is unclear, because study supplementation has varied between 0.36-5 mgs/day
- Folic acid supplementation no less than 0.4mgs/day pre pregnancy and through pregnancy
CASE 3

- 17 year old male evaluated with a first GTC seizure
- Occurred in the morning shortly after waking up
- Preceded by myoclonic jerks of arms
- Neurological and general exam are normal
- Blood work and MRI of the brain with gadolinium were normal
BONE HEALTH

- People with epilepsy have a higher rate of broken bones than people who do not have seizures.
- Fractures are 2-6 times more frequent in patients with epilepsy compared to the general population.
Enzyme inducing AEDs: Phenytoin, Phenobarbital, Primidone are associated with decreased Bone Mineral Density

Carbamazepine increases bone turnover

Enzyme inducing agents demonstrate

- Lower vitamin D levels
- Increased bone specific alkaline phosphatase
BONE HEALTH

Severity may be correlated with:

- Duration of AED exposure
- Number of AEDs used
- Type of AEDs used
- Inducers of cytochrome P450 most commonly associated w/ bone disease:
  - Phenobarbital
  - Phenytoin
  - Primidone
  - Carbamazepine
  - Possibly VPA
BONE HEALTH

- AEDs may decrease bone mineral density
- Alter bone mineral metabolism
- Women in particular are vulnerable to the effects of AEDs on bone health
- Women taking AEDs are two times more likely to have hip fracture (study women older 65)
BONE HEALTH

- In women with epilepsy osteoporosis appears to be more prevalent
- Occurs at younger age
Progressive bone deficit in epilepsy

- A cross-sectional evaluation
- 82 ambulatory children aged 6 to 18 years
- With epilepsy for <1 year to 6 or more years (n = 27)
- Controls were 32 healthy children aged 12.8 ± 2.6 years
Progressive bone deficit in epilepsy

- Children with epilepsy had reduced total body mean bone mineral density compared with control.
- Increasing duration of epilepsy was associated with a reduction in total bone mineral density.
- Boys < 1 year of epilepsy higher bone density than girls.
Progressive bone deficit in epilepsy

- > 6 or more years of epilepsy girls had higher bone density compared with boys
- Both boys and girls with epilepsy are at risk for lower bone density
- The study was not powered to determine individual antiepileptic medication effects on bone mineral density
All patients with epilepsy should receive adequate daily CA and vitamin D

Regular exercise gravity resisting

All menopausal women and patients with prolonged AED use (>5 years), should have a DEXA scan
BONE HEALTH

Bone disease is increased:

- With history of enzyme inducing AEDs exposure
- Polypharmacy
- Longer duration of treatment
BONE HEALTH

- Significant declines in bone density can be seen 1 year after initiation of AEDs.
- The appropriate timing for the first screen or interval for subsequent follow up is unknown.
- Some suggest to screen for patients on AEDs for 2-5 years.
EPILEPSY AND ALCOHOL

- Moderate alcohol consumption is not associated with increased seizure activity.
- Binge drinking and alcohol withdrawal can cause seizures and even status epilepticus.
- A drink or two now and then does not increase seizure activity.
- When alcohol is related to seizures, usually are secondary alcohol withdrawal rather than drinking itself.
- Alcohol withdrawal seizures 6 and 72 hours after the last drink.
- Risk of seizures is increased after three or more alcoholic beverages.
EPILEPSY AND EXERCISE

- Aerobic
- Walking
- Jogging, running (especially on an indoor, grass, or supervised track)
- Stationary bicycling (recumbent bicycle) are particularly safe
- Treadmills are generally safe (emergency stop)
- Elliptical or similar devices are probably preferable to treadmills
- Exercise benefits individuals with epilepsy: including improved seizure control, mood, and quality of life
- No significant evidence to suggest that contact sports are harmful to athletes with epilepsy
CASE 3

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AED CHOICE

- Phenobarbital
- Phenytoin
- Primidone
- Carbamazepine !!!
- Oxcarbazepine !!!
- Topiramate
- Rufinamide
- Felbamate

- Valproic Acid
- Gabapentin
- Lamotrigine
- Tiagabine
- Zonisamide
- Levetiracetam
- Lacosamide
- Pregabalin
- Vigabatrin
- Ezogabine
ALWAYS DISCUSS SEIZURE PRECAUTIONS
KEEP AN EYE ON THE GOAL

GOALS OF THE TREATMENT

– Seizure freedom
– Good quality of life
– No side effects