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**1<sup>st</sup> and 2<sup>nd</sup> Generation  
Antiepileptic Drug  
Use in the ED:  
*Optimal 2007 Strategies***

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**ACEP  
Scientific Assembly**

**New Orleans, LA  
October 16-18, 2006**

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**Disclosures**

- NovoNordisk, King Pharmaceuticals, UCB Pharma Advisory Boards
- Eisai Speakers' Bureau
  
- ACEP Clinical Policies Committee
- ACEP Scientific Review Committee
- Executive Board, Foundation for Education and Research in Neurologic Emergencies
- FERNE support by Abbott, Eisai, Pfizer, UCB

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## Key Clinical Questions

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- What ED seizure and SE patient types might be optimally treated through the use of a first or second-generation AED based on the stated priorities and options?
- What recommendations can be made regarding the ED use of 1st and 2nd generation AEDs in 2007?

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## A Clinical Case

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## Patient EMS Data

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- 50?? yo male John Doe
- Generalized tonic-clonic seizure
- Chicago Fire Department
- Diazepam 5 mg IM, 15 mg IV
- Seizure continuous for 15 minutes +
- EMS to ED
- No change in status

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## Patient Clinical History

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- Unknown meds
- Unknown medical history
- Hx Needs surgery next month ??
- EtOH ??
- Does not appear to be homeless
- Accucheck 119

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## ED Presentation

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- Facial and shoulder twitching R
- Pt with gurgling BS
- Nasopharyngeal airway
- No evidence of trauma or toxicity
- IV access in neck
- Seizure persists x minutes

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## Why Consider This Case?

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- Status epilepticus: medical emergency
- Few hospitals utilize a SE protocol
- SE protocol improves patient outcome
- Guidelines exist that facilitate practice
- New useful medications exist
- SE provides a model for all AED use

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## **Seizure Rx: *Key Concepts***

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- AED indications described
- AEDs provide not only acute seizure Rx, but also epilepsy Rx
- AED selection based on efficacy, safety, tolerability, clinical effectiveness, cost (not generation)
- ED AED use based on clinically relevant key concepts

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## **Seizure Classification**

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## **Seizure Types**

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- **Generalized:** both cerebral hemispheres
- **Partial:** localized to within one cerebral hemisphere

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## **Generalized Seizures**

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- **Convulsive:** tonic-clonic
- **Non-convulsive:** absence

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## **Generalized Seizures**

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- **Primary generalized:** starts as generalized seizure
- **Secondarily generalized:** seizure has a partial onset, as with an aura, then generalizes

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## **Partial Seizures**

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- **Simple partial:** no impaired consciousness
- **Complex partial:** impaired consciousness

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## Sz Pt ED Clinical Settings

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- Isolated uncomplicated seizure
- Flurry of seizures, SE risk
- Status epilepticus
- Refractory SE

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## AED Indications

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- Active seizure
- Status epilepticus
- New onset seizure
  
- Recurrent seizures, epilepsy
- Established epilepsy patient
- Refractory epilepsy patient

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## Seizure vs. Epilepsy Pts

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- Emergency physicians treat acute seizure and SE patients
- Neurologists and other long-term providers treat epilepsy patients
- Although the patients are the same, the priorities may differ
- Can AED selection address both sets of priorities?

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## AED: Efficacy & Safety

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- Does the AED stop seizures?
- Does the AED prevent seizures?
- Does the AED provide efficacy without causing adverse events that cause harm or limit clinical effectiveness?

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## AED: Tolerability

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- Do patients take the AED over time because it achieves better health?
- Are seizures prevented without intolerable side effects?

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## AED: Clinical Effectiveness

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- Is the AED safe with proven efficacy?
- Do patients take the AED over time because it provides better health?
- Do clinicians use the AED because it provides quality patient care and enhances their clinical practice?

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## AED: Cost

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- Is the AED cost justified based on the efficacy, safety, tolerability, and clinical effectiveness?
- Is someone willing to pay the cost of the AED?

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## ED AED Use: Priorities

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- Prevent or stop acute ED seizures
- Prevent or treat SE in the ED
- Prevent seizures or SE from occurring after disposition
- Prescribe AEDs that support the treatment of the epilepsy patient and the work of the follow-up physicians in prescribing AEDs

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## ED AEDs: Key Concepts

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- Standard treatment paradigm exists for ED seizure and SE patients
- Limited parenteral AEDs available
- Oral AEDs can be utilized
- Choice in ED prioritizes acute seizure Rx

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## ED Seizure SE Treatment

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- Benzodiazepines
- Phenytoins
- Bolus infusion AEDs
  - Levetiracetam, Phenobarbital, Valproate
- Continuous infusion AEDs
  - Midazolam, Pentobarbital, Propofol

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## Benzodiazepines

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- Diazepam, lorazepam, midazolam
- Diazepam: short-acting, low risk pts
- Lorazepam: long-acting, at risk pts
- Midazolam: best IM parenteral benzodiazepine AED
- Midazolam useful as continuous infusion in refractory SE

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## Phenytoins

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- Fosphenytoin, phenytoin
- Fosphenytoin: water soluble, prodrug, phenytoin is active moiety
- Phenytoin: toxic diluents, Na<sup>+</sup> channel control of partial onset seizures
- Commonly utilized 1<sup>st</sup> generation AED

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## Fosphenytoin

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- Rapid infusion, but therapeutic free phenytoin level no sooner (minutes)
- Rapid infusion in SE facilitates quicker next AED choice and rapid progression through an established SE protocol
- May enhance safety margin in patients with poor IV access
- IM use enhances ED utility

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## Fosphenytoin

- Pruritus not a histamine mediated response, it is related to prodrug
- Slow infusion rate, no diphenhydramine
- Therapeutic level 10-20  $\mu\text{g}/\text{ml}$
- Careful phenytoin level determination
- No level within 2 hrs of IV & 4 hrs of IM use
- Therapeutic level within 30 minutes if IM load provided

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## Bolus Infusion AEDs

- Levetiracetam, phenobarbital, valproate
- Should these meds be given parenterally if the patient is on these meds orally?
- This is the approach with phenytoin
- Should these be given prior to phenytoin?
  - Advantage: No addition of another AEDs
  - Disadvantage: No clear efficacy with a flurry of seizures (SE risk) or when treating SE
- What if no therapeutic level data exists?

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## Levetiracetam

- New parenteral second generation AED
- Useful as adjunct in partial seizure Rx
- Not approved as monotherapy or in SE
- (Same is true for all 2<sup>nd</sup> generation AEDs)
- Therapeutic level cannot be obtained
- Same oral & IV parenteral bioavailability
- May have enhanced tolerability and similar efficacy to phenytoin in epilepsy pt Rx
- Increased cost

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## Phenobarbital

- Very useful AED, third drug in SE protocol
- Few epilepsy patients are on this AED as monotherapy (less clinical effectiveness)
- Therapeutic level 15-40  $\mu\text{g}/\text{ml}$
- When utilized in seizure patient with an uncomplicated sz, oral loading is the norm
- In SE, bolus dosing will often immediately precede intubation due to sedation

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## Valproate

- Parenteral generation AED, now generic
- Limited ED knowledge of parenteral use
- Should it be given prior to phenytoin in at risk seizure patients on oral Depakote?
- Will it work to prevent or treat SE?
- Therapeutic level 50-125  $\mu\text{g}/\text{ml}$
- For every 1  $\text{mg}/\text{kg}$  loaded, therapeutic level will increase by 5  $\mu\text{g}/\text{ml}$
- Supra-therapeutic level in SE is OK

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## Oral AED Loading

- Not inferior when phenytoin loading
- Consider if similar PO bioavailability
- May be a less useful priority if SE possible or if disposition home from ED
- Allows greater second generation AED use
- Uncertainty if therapeutic level cannot be obtained to guide dosing decisions
- Usually guided by neurology consultation

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## ED Patient Outcome

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## ED Patient Management

- Lorazepam 2 mg IVP x 5 over 10 minutes
- Persistent facial and R shoulder activity
- AMS: generalized seizure continues
- Fosphenytoin 1 gram PE over 10 min
- Fosphenytoin 1 gram PE over 10 min
- Seizure ended, pt remained obtunded
- Intubation immediately followed
- Lidocaine, sux, rocuronium

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## ED Diagnostic Evaluation

- Non-contrast CT: Prior strokes, atrophy
- Metabolic tests normal
- Toxicology screening negative
- Phenytoin level cancelled
- Diagnoses:
  - AMS
  - Status Epilepticus
  - Respiratory Failure

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## Family Arrives, Pt History

- Pt with history refractory seizures
- Hx carotid artery occlusion R
- Due for carotid endarterectomy
- Phenobarbital & dilantin, compliant
- Prior history of SE treated at UIC
- No medic alert bracelet
- No recent illness, trauma, EtOH

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## Patient Outcome

- EEG in ED, within 150 minutes
- Neuro consultation, no subtle SE
- Admit to Neuro ICU
- Repeated doses of rocuronium
- Final disposition for carotid Rx

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## Conclusions

- ED seizure patient Rx needs to address both the immediate seizure and the long-term epilepsy management
- In general, ED seizure patient Rx focuses on parenteral AED use
- Oral Rx, 2<sup>nd</sup> generation AEDs useful
- Must understand principles that govern ED AED use and priorities of those that provide long-term epilepsy Rx

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## Recommendations

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- Be able to identify the seizure type and optimal patient therapies based on etiology, demographics, and risk/benefit
- Establish seizure and SE protocol
- Understand fully the optimal use of parenteral and 2<sup>nd</sup> generation AEDs
- Stop the acute seizure & prevent SE
- Wisely prescribe so that follow-up epilepsy management can be optimized

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## Questions?

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10/31/2006 4:47 PM

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