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**Managing Seizure Patients in SE Following the Use of the Benzodiazepines**

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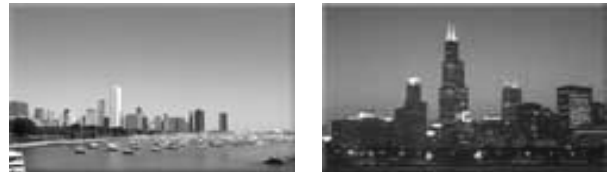
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**Global Objectives**

- Improve care of the patient with SE
- Minimize morbidity and mortality
- Expedite disposition
- Optimize resource utilization
- Enhance our job satisfaction
- Maximize Rx options, success

### Sessions Objectives

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- Review seizure and SE epidemiology
- Address non-response to benzos
- Examine role of Rx's after benzos
  - IV phenytoins
  - IV phenobarbital
  - IV valproate
  - IV propofol
  - Continuous IV benzodiazepine infusions
- Provide conclusions regarding Rx

### Clinical History

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A 37-year old male is brought to the emergency department by EMS because of a seizure at home upon awakening. The patient had a generalized tonic-clonic seizure that lasted several minutes and spontaneously resolved, followed by a period of unresponsiveness during EMS transport. The patient is known to have a history of post-traumatic seizures that are managed with phenytoin and phenobarbital. The family stated that the patient has had neither recent illness nor head trauma. The family stated that they believed the patient was compliant with his medications, although non-compliance has been an issue in the past.

### ED Presentation

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In the Emergency Department, the patient begins to respond to questions, but is still somewhat post-ictal. On initial exam, there are neither focal neurological findings nor any evidence of any other medical condition that would precipitate a seizure. The patient then has another generalized seizure with tonic-clonic seizure activity. The seizure lasts several minutes while medications were being obtained.

### Seizure Epidemiology

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- 2.5 million people with epilepsy
- 6.6 per 100,000
- 28% visit an ED annually
- 150,000 new onset seizures per year
- 1-2% of all ED visits for seizures
- 2 millions ED visits per year

### Status Epilepticus Epidemiology

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- 50,000-150,000 Cases annually
- 50 Cases per 100,000 population
- Infants and elderly: greatest risk
- Etiol: acute insult, epilepsy, new onset sz
- Mortality 5-22%, 65% with refractory SE
- 7% of ED seizure patients in SE
- ED physicians: 5 SE cases per year

### Seizure Rx with Benzodiazepines

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- What percent of ED seizure patients will not respond to initial treatment with benzodiazepines?
- How many patients will not respond to initial EMS or ED Rx?

### Status Epilepticus Mechanism

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- Abnormal discharge by a few unstable neurons
- Propagation by recruitment of normal neurons
- Failure of normal inhibitory neurotransmitters (GABA)
- Enhancement of excitatory neurotransmitters
  - (glutamate, aspartate, acetylcholine)
- Interference with normal metabolic processes
  - glucose, O<sub>2</sub> metabolism
  - Na<sup>+</sup>, Ca<sup>++</sup>, K<sup>+</sup>, Cl<sup>-</sup> ion shifts

### SE Duration and Mortality

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- SE >60 min: 10-fold greater 30-day mortality (32% vs 2.7%)
- Worse outcome associated with
  - Longer duration SE
  - SE refractory to first-line therapy

### Refractory Seizures: ED Exp

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- Huff: Prospective ED seizure study
  - 17% of sz patients: repeat seizure
  - 6% of sz pts: Dx with SE
- EMS seizure patients
  - 7% found to be actively seizing
  - 1% actively seizing at ED arrival

### Refractory Seizures: ED Exp

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- Pre-hospital Trial of SE (PHTSE)
  - SE population
  - 41-79% active sz upon ED arrival
- ED pediatric seizure patients
  - 5-7% of pts will seize in the ED
  - Independent of febrile, afebrile etiol

### Conclusions: ED Seizures

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- 1-2% Active seizing at ED arrival
- 41-79% Active seizing in EMS SE
- 5-17% of ED pts will repeat seize
- 6% of sz pts will be Dx'd with SE

### Refractory Seizures : Trials

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- Prospective, randomized clinical trials
- Leppik, 1983: Benzos seizure control
  - 89% control with lorazepam (no stat diff)
  - 76% control with diazepam
- Treiman, 1998: VA SE study
  - 67% control with lorazepam (no stat diff)
  - 60% control with diazepam, phenytoin

### Refractory Seizures : Trials

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- Alldredge, 2001: PHTSE
  - 59% control with lorazepam \*\*
  - 43% control with diazepam \*
  - 21% sz termination in placebo group
- Treiman, 1990: Benzo overview
  - 79% control with benzos
  - Based on review of 1,346 study patients

### Conclusions: Refractory Sz Trials

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- 59-89% Sz control with lorazepam
- 43-76% Sz control with diazepam
  
- Lorazepam superiority suggested

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Phenytoins
  - Phenobarbital
  - Valproate
  - Propofol
  - IV Benzodiazepine infusions
  - Pentobarbital

### Status Epilepticus Definition

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- Needed for epidemiologic and clinical trials
- Historical definitions
  - Two seizures within 30 min, no a lucid interval
  - One seizure >30 min duration
- More recent definitions more aggressive
  - Two seizures over any interval, no lucid interval
  - One seizure of >10 min duration

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Phenytoins

### Seizure Rx: Phenytoins

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- IV phenytoin
- IV fosphenytoin
- High-dose phenytoins

### Seizure Rx: Phenytoin

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- Few trials of phenytoin in SE
- Treiman 1998: VA SE study
  - 56% success: diazepam, phenytoin
  - 20 min endpoint, EEG termination
  - Difference with fos-phenytoin?

### Seizure Rx: Fosphenytoin

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- Fosphenytoin in SE
- Most rcv'd benzos, SE terminated
- 97% remained sz-free for 2 hours
- No prospective studies in active SE
- Rates up to 150 mg/min shown

### Seizure Rx: Fosphenytoin

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- Rapid infusion in SE
- Use as a resuscitation drug
- Less toxic diluent
- Infusion into less reliable IV access
- IM injection when no IV access

### Seizure Rx: High-dose Phenytoins

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- Osorio, 1989: 13 SE patients
  - Mean dose 24 mg/kg
  - 38% did not require phenobarbital
  - 62% success rate
- Epilepsy Foundation of America, 1993
  - Working group recommendations
  - Use up to 30/mg/kg prior to other Rx

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Phenobarbital

### Seizure Rx : Phenobarbital

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- Accepted Rx, 2 non-blinded studies
- Shaner, 1988: DZ/PHT, PB/prn PHT
  - SE duration shorter with PB
  - 61% of PB pts required no PHT
- Painter, 1999: Neonatal seiuires
  - Compared PB, PHT for active sz
  - PB 57%, PHT 62% as monotherapies

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Valproate

### Seizure Rx : Valproate

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- Giroud, 1993: French SE series
  - 83% success in terminating SE
  - Other drugs were provided prior
- Case series have shown efficacy
- Rates up to 300 mg/min shown

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Propofol

### Seizure Rx : Propofol

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- Stecker, 1998: propofol vs. barbs
  - Fewer SE pts controlled (63 vs. 82%)
  - Control time shorter (3 vs. 123 min)
- Other series have shown efficacy
- Provides burst suppression
- Must be D/C'd slowly

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Continuous benzodiazepine infusions

### Seizure Rx : Continuous Benzos

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- Singhi, 2002: diazepam vs. midazolam
  - 40 pediatric patients, 6 hours sz-free
  - Equal efficacy in SE control (86%, 89%)
  - Midazolam: higher recurrence, mortality

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Midazolam

### Seizure Rx : Midazolam

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- Midazolam vs. propofol vs. pentobarbital
  - Midazolam 80% effective
  - Greater rates of breakthrough seizures
    - (51 vs. 15 vs 12%, respectively)
  - Lower risk of hypotension (30 vs. 44 vs. 77%)
- IV Midazolam in 40 patients, two studies
  - 33 pts non-convulsive SE: 82% efficacy
  - 67% in another study of SE

### Seizure Rx after Benzos

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- What is the role of the following second line Rx in SE patients?
  - Pentobarbital

### Seizure Rx : Pentobarbital

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- Pentobarbital vs. propofol:
  - 82% vs. 63% efficacy
  - Pentobarb longer to SE termination (123 vs. 3 min)
- Pentobarbital vs. propofol vs. midazolam
  - 92% effective: vs. 80% midazolam, 73% propofol
  - Highest hypotension seen with pentobarbital: 77%
  - Compared to 42% propofol, 30% midazolam

### Seizure Rx : Pentobarbital

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- Pentobarbital most effective with certain SE etiologies
  - Chronic epilepsy, infection, tumors, stroke, trauma
  - 91% efficacy
  - Anoxia, toxic/metabolic
  - 29% efficacy

### Seizure and SE Rx : Class A Recs

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- Seizures and SE: two choices
  - Diazepam then phenytoins
  - Lorazepam
- Lorazepam may be superior

### Seizure and SE Rx : Class B Recs

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- Peds seizures, SE: IV lorazepam
  - Reduced respiratory compromise
  - Not true of other parenteral diazepam
- Phenobarbital or phenytoins OK

### Seizure and SE Rx : Class C Recs

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- High dose phenytoins (30 mg/kg)
- Fosphenytoin if rapid, high risk, IM
- Rapid IV valproate if hypotensive
- IV propofol or IV midazolam for refractory SE
- IV pentobarbital also an option

### Conclusions: Seizure and SE Rx

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- Limited studies support Rx choices
- Phenobarbital studies: best data
- Current recommendations:
  - Benzos, phenytoins, phenobarbital
  - Valproate, propofol also useful

### Conclusions: Seizure and SE Rx

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- Rapid infusion: fos-phenytoin, valproate
- Limited supply of phenobarbital
- IV valproate: limited sedation
- Propofol: burst suppression

### Conclusions: SE and its Therapies

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- Refractory to benzodiazepines: SE
- Rare, but significant M & M
- Many therapies can be used
- Varied risks and benefits of each Rx

### Recommendations: SE ED Rx

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- Have your drugs available in ED
- Have a protocol with times
- Rapidly go thru drugs in protocol
- Provide full mg/kg doses
- Use all of these drugs in 75-90 min

### **SE Protocol: An Example**

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- 0 - 20 min: Initial Rx, benzos
- 20 - 40 min: Phenytoins
- 40 - 60 min: Phenobarbital
- 60 - 75 min: Valproate
- 75 - 90 min: Propofol

### **SE Recommendations**

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- Develop a SE protocol
- Make all therapies available
- Make EEG a “stat” test
- Work with neurologists, NS
- Optimize SE patient outcome

### **ED Rx in Status Epilepticus: ED Management of the Clinical Case**

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The patient is initially treated with four doses of IV lorazepam, to a total dose of 8 mg, which is approximately 0.1 mg/kg. However, the patient continues to seize. The airway is patent with adequate vital signs and pulse oximetry readings. The patient is then given a rapid infusion of one gram of fosphenytoin over 10 minutes, and then receives a second infusion of 500 mg of fosphenytoin over five minutes. The generalized seizure then stops.

### **ED Rx in Status Epilepticus: ED Management of the Clinical Case**

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The patient is stable but remains unresponsive for over 30 minutes in the ED while an ICU bed is being obtained. Cardiopulmonary, metabolic and toxicology tests are negative, as is a non-infused CT of the head. The initial levels of both phenytoin and phenobarbital were found to be sub-therapeutic.

### **ED Rx in Status Epilepticus: Hospital Course & Disposition**

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An EEG is arranged for and is completed upon arrival to the ICU, within about 120 minutes of the seizure onset in the ED. The patient is consulted by a neurologist, and is found not to be in subtle status epilepticus based on the EEG result and neurologic exam.

### **ED Rx in Status Epilepticus: Hospital Course & Disposition**

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The patient awoke completely within 12 hours and was discharged from the ICU the next day without any morbidity related to this prolonged seizure. The patient was discharged home two days later with the instructions to take his medications as prescribed, with neurology follow-up one week later.

### **Recommendations**

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- **Class A:**  
Treat patient who are actively seizing either with intravenous lorazepam or diazepam.
- **Class B:**  
None specified.
- **Class C:**  
In patients with refractory status epilepticus that do not respond to benzodiazepines, administer one of the following agents intravenously: high dose phenytoin, midazolam, pentobarbital, phenobarbital, propofol or valproic acid.

### **Questions??**

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