SEIZURE SYNDROMES
SEIZURE SYNDROMES

• Caused by any alteration of the central nervous system→
  ◦ An uncontrolled, hypersynchronous, acute neuronal discharge, originating in the cerebrum, brain stem, or spinal cord, w/ variable spread→
    – Syndrome according to the stimulated region(s)

Statistics:
• Occurs in 7% of the population, w/ epilepsy (any chronic seizure disorder) affecting 1% of the population

RISK FACTORS

• Cerebrovascular accident
  ◦ Ischemic
  ◦ Hemorrhagic

• Hyperthermia

• Illicit drugs
  ◦ Alcohol withdrawal
    – 50% first experienced within 24 hours after abrupt dose reduction
  ◦ Amphetamines
  ◦ Cocaine

• Infection
  ◦ Encephalitis
  ◦ Meningitis

• Intracranial tumor

• Metabolic disorder
  ◦ Hypocalcemia
  ◦ Hypomagnesemia
  ◦ Hyponatremia
  ◦ Hypoxemia
  ◦ Hypo or hyperglycemia
  ◦ Hyperosmolarity
  ◦ Uremia, via either:
    – Renal failure→↑ creatinine, urea, & uric acid
- Hepatic failure → ↑ammonia
  - Porphyria
  - Post–traumatic
    - Head injury
    - Intracranial surgery
  - Pregnancy
    - Eclampsia
  - Medications
    - Local anesthetics (ex: Lidocaine)
    - Antibiotics
      - Ciprofloxacin
      - Imipenem
      - Isoniazid–INH
      - Penicillins
    - Anticholinesterases
    - Antidepressants
    - Antihistamines
    - Antipsychotics
    - Aspirin
    - β receptor blockers
    - Cyclosporine
    - Hypo–osmolar parenteral solutions
    - Lithium
    - Methylxanthines (Aminophylline, Theophylline)
    - Phencyclidine
    - Sympathomimetic medications
  - Vascular malformations
    - Aneurysm
    - Arteriovenous malformation
  - Vasculitis
  - Withdrawal of medications
    - Antiseizure medications
    - Barbiturates
    - Benzodiazepines
    - Opiates
• Idiopathic
• Febrile convulsions of childhood
• Subtherapeutic plasma level of antiseizure medication
  • Postictally, the cerebrospinal fluid may contain more cells than normal, termed pleocytosis, w/ the count being \( \leq 80 \text{ cells/} \mu\text{L} \), w/ either a polymorphonuclear or mononuclear predominance in:
    • 2% of patients after a single tonic &/or clonic seizure
    • 15% of patients after status epilepticus
  …in the absence of infection

CLASSIFICATION/ DIAGNOSIS

FOCAL SEIZURES
• Neuron depolarization→
  • Spreading, localized reverberating circuits→synchronous, focal depolarization over adjacent grey matter regions, w/ consciousness being either:
    – Preserved, termed simple focal seizures
    – Impaired, termed complex focal seizures
  …but not lost, unless secondary generalization occurs

Potential additional features:
• Simple focal seizures may progress to complex focal seizures
• Secondary generalization throughout the ipsilateral & contralateral hemispheres→
  • Tonic–clonic seizure
• Temporary paralysis, termed Todd’s paralysis, of affected regions being either:
  • Incomplete, termed paresis
  • Complete, termed plegia
  …usually being unilateral, lasting hours to days, potentially occurring after any seizure type affecting the motor cortex, which can also affect speech, vision, &/or swallow function

SIMPLE FOCAL SEIZURES
• **Motor**
  - Focal muscle contractions
  - Progressive, successive, motor cortex depolarization, termed a **Jacksonian seizure**
    - March of contractions, according to the motor homunculus

• **Sensory**, indicating a **parietal lobe seizure**
  - Somatosensory
    - Paresthesias, esp. tingling & numbness
  - Auditory
    - Buzzing
  - Gustatory
    - Bad taste
  - Olfactory
    - Bad smell
  - Vertiginous
    - Dizziness
    - Vertigo
  - Visual
    - Flashing lights
    - Changing object size &/or distance

• **Autonomic**
  - Vasoconstriction
    - Pallor
  - Vasodilation
    - Flushing

• **Psychic**
  - Anxiety
  - Dream-like feelings of unreality
  - Fear
  - Recurrent perceptions, being either:
    - Familiar, termed déjà vu
    - Unfamiliar, termed jamais vu

• **Mixed**
≥ 2 of the above

COMPLEX FOCAL SEIZURES
• Staring (indicating a temporal lobe seizure in 75% of patients) ± automatisms:
  ◦ Blinking
  ◦ Chewing
  ◦ Fidgeting
  ◦ Hand rubbing
  ◦ Lip smacking
  ◦ Picking movements
  ◦ Walking

GENERALIZED SEIZURES
• Generalized neuron depolarization throughout the ipsilateral & contralateral hemispheres→
  ◦ Sudden loss of consciousness, except w/ most myoclonic seizures

• Absence seizure
  ◦ Postural tone is maintained, w/ < 30 seconds of motionless staring ± momentary spasmodic muscle contractions, termed twitches (usually involving the head, esp. blinking), w/ subsequent regained consciousness & resumption of previous activity, without post–seizure (also termed postictal) confusion or lethargy
  – Usually begins in childhood, w/ regression by age 30
  – May occur rarely or frequently throughout the day
  – May be induceable by any flickering light source &/or hyperventilation

Potential additional features:
• Altered generalization throughout the ipsilateral & contralateral hemispheres→
  ◦ Tonic–clonic seizure

• Tonic–clonic seizure
  ◦ Tonic seizure via global skeletal & smooth muscle contraction→
–Body stiffening→fall
–Exhalation→loud wheeze
–Teeth clenching→tongue &/or cheek biting
–Upward rolling of opened eyes
–Urination
–Defecation

...followed by a **clonic seizure** via spasmodic muscle contrac-
tions→
  • Body jerking
  • Episodic exhalation→
    ◦ Grunting
  • Teeth clenching→
    ◦ Tongue &/or cheek biting
...w/ the entire seizure lasting **several seconds to minutes**, w/ post–seizure nervous system depression→
  • Confusion
  • Severe fatigue→
  – Hours of sleep

**Potential additional features:**
• Temporary **paralysis**, termed Todd’s **paralysis**, of affected re-
  gions being either:
  ◦ Incomplete, termed paresis
  ◦ Complete, termed plegia

...**usually being unilateral**, lasting hours to days, potentially
  **occurring after any seizure type affecting the motor cor-
  tex**, which can also affect speech, vision, &/or swallow func-

• Other
  ◦ Tonic seizure
  ◦ Clonic seizure
  ◦ Myoclonic seizure
    – Single or repetitive bilateral rapid limb contractions, **usually**
      w/ preserved consciousness
  ◦ Atonic seizure
Sudden loss of muscle tone→fall, defecation, & urination

EPILEPSY

• Any chronic seizure disorder
  ◦ Tonic clonic seizures→40%
  ◦ Complex partial seizures→40%
  ◦ Simple partial seizures→15%

• All patients w/ epilepsy must have their condition reported to the department of motor vehicles→DMV

PSEUDOSEIZURE

• Done in an attempt to:
  ◦ Avoid responsibility &/or other undesired situations
  ◦ Gain sympathy &/or compensation

→faked seizure-like syndrome, termed malingering, usually being atypical, w/ purposeful movements, including:
  • Thrashing, rather than jerky limb movements
  • Pelvic thrusting
  • Opisthotonic posture
  • Deep breathing
  • Eyes held tightly shut
  • Retained consciousness→
    ◦ Emotional reactions
    ◦ Meaningful speech
    ◦ Response to verbal instruction
    ◦ Lack of post→seizure confusion or fatigue
    ◦ Recall for periseizure events

• If you suspect pseudoseizures in an unconscious patient, raise the patients arm, high over their face & allow it to drop. A patient w/ pseudoseizures will usually not allow the arm to hit their face

STATUS EPILEPTICUS

• A medical emergency of either:
  ◦ Persistent seizure
  ◦ Recurrent seizures without intervening recovery to baseline
consciousness
…which may occur w/ any seizure type, though usually referring to tonic &/or clonic seizures, for which the following pertains:

Statistics:
• Occurs in 60,000–160,000 persons/ year, w/ the majority occurring in the pediatric age group (esp. age ≤ 5 years)
• The #1 cause in adults is a cerebrovascular accident (ischemic &/or hemorrhagic)
• 50% of cases occur as new–onset seizures

Cardiovascular
• ↑Autonomic sympathetic tone
  • Tachycardia
  • Hypertension
  • Diaphoresis
• Dysrhythmia via either:
  • Hyperkalemia
  • Hyperthermia
  • Metabolic acidemia

Musculoskeletal
• Continuous muscle contraction
  • ↑Myocyte metabolism
    – ↑Heat production → ↑core temperature, termed hyperthermia
• Fall &/or continuous muscle contraction
  • Head &/or extremity trauma
    – Bruising
    – Lacerations
    – Fractures
    – Shoulder dislocations

Pulmonary
• Ineffective respiratory effort
  • Hypercapnic respiratory failure

Hematologic
• Stress induced neutrophil demargination
  • Leukocytosis
• Continuous muscle contraction
  ◦ ↑Myocyte metabolism
    – Lactic acidemia mediated metabolic anion gap acidemia
• Skeletal muscle death, termed rhabdomyolysis
  ◦ Rapid release of intracellular contents
    – Acute renal failure
    – Electrolyte abnormalities

**ELECTRICAL STUDIES**

• Electroencephalography–EEG
  Indication:
  • To localize & classify a seizure syndrome
  • Emergently if concerned about possible nonconvulsant status epilepticus
  Findings:
  • Focal seizures: Focal deranged pattern
  • Absence seizures: Spike & dome wave pattern over most or all of the cerebral cortex
  • All other generalized seizures: Spike wave pattern over most or all of the cerebral cortex
  Mechanism:
  • Scalp electrodes register cortical brain electric potentials, w/ intensity & frequency determined by the level of cortical excitation, always being abnormal during & immediately after a tonic–clonic seizure
  Outcomes:
  • Sleep deprivation
    ◦ ↑Sensitivity & specificity
  Limitations:
  • Is often normal between seizures = interictally
  • May miss a focal seizure, especially those occurring:
    ◦ In the interhemispheric fissure
    ◦ Outside of the cerebral cortex

**CHRONIC TREATMENT**
Indications:
• Identified persistent etiology
• Idiopathic w/ either:
  ○ Status epilepticus
  ○ Todd’s paralysis
  ○ Focal neurologic finding
  ○ Abnormal electroencephalogram

• Patients should be instructed not to:
  ○ **Drive** or operate hazardous machinery
    – The required duration of time without seizures in order for
      someone w/ epilepsy to regain driving privileges varies across
      the states, from 3months to 1year
  ○ Take baths or swim
  ○ Perform any task in which a seizure is likely to harm them or others

• Anti–seizure medications are classified as either:
  ○ **Broad spectrum**: Felbamate, Lamotrigine, Levetiracetam, Topiramate, Valproic acid, Zonisamide
  ○ **Narrow spectrum**: Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin
    … based on efficacy against various seizure types

• **Focal seizures ±** secondary generalization
  ○ **All antiseizure medications are considered of equal efficacy**

• **Generalized seizures**: The medications listed for each seizure type are considered roughly equivalent in efficacy, w/ preference being based on ease of use, side effects, & cost
  ○ **Tonic &/or clonic seizures**
    – First line: Lamotrigine, Levetiracetam, Valproic acid
    – Second line: Carbamazepine, Oxcarbazepine, Phenytoin, Topiramate, Zonisamide
  ○ **Absence seizures**
    – First line: Ethosuxamide, Valproic acid
- Second line: Clonazepam, Lamotrigine, Levetiracetam, Zonisamide

**Myoclonic seizures**
- First line: Lamotrigine, Levetiracetam, Valproic acid
- Second line: Clonazepam, Felbamate, Topiramate, Zonisamide

### ANTISEIZURE MEDICATIONS

- **Monotherapy being preferred**, w/ most experts recommending several attempts at monotherapy prior to combination treatment
- Being that many antiseizure medications have a relatively narrow therapeutic window between the effective dose & toxicity (unlike other medications), substitution of trade to generic versions should be undertaken w/ caution. If possible, generic refills should come from the same manufacturer

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♂: Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong> (Tegretol)</td>
<td>LK/ U: 200mg PO q12hours, then titrate to a therapeutic plasma level of 4–12µg/ mL (800mg q12hours)</td>
</tr>
<tr>
<td>• XR form</td>
<td></td>
</tr>
<tr>
<td><strong>Clonazepam</strong> (Klonopin)</td>
<td>LK/ U: 0.5mg PO q8hours, then titrate to a therapeutic plasma level of 20–80 ng/ mL (3mg q8hours)</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong> (Zarontin)</td>
<td>LK/ ?: 500mg PO q24hours, then titrate to a therapeutic plasma level of 40–100µg/ mL (1.5g/ 24hours)</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong> (Lamictal)</td>
<td>LK/ ?: 25mg PO q24hours (350mg q12hours†)</td>
</tr>
<tr>
<td><strong>Levetiracetam</strong> (Keppra)</td>
<td>K/ ?: 500mg PO q12hours (1.5mg q12hours)</td>
</tr>
<tr>
<td><strong>Oxcarbazepine</strong> (Trileptal)</td>
<td>LK/ ?: 300mg PO q12hours (1.2g q12hours)</td>
</tr>
</tbody>
</table>
| **Phenytoin** (Dilantin) | L/ U: 400mg PO, then 300mg PO q2hours X 2 = 1g total loading dose, then 300mg PO q24hours (500mg q24hours max), then titrate to a therapeutic plasma level of:
  • Total: 10–20µg/ mL‡
  • Free: 1–2µg/ mL⁄ |
| • XR form | |
| **Topiramate** (Topamax) | K/ ?: 25mg PO q12hours (200mg PO q12hours) |
Valproic acid (Depakote)
• XR form
  500mg PO q24hours, then titrate by 250mg PO q24hours, qweek to a therapeutic plasma level of 50–150µg/ mL (3.5g/ 24hours)

Zonisamide (Zonegran)
• 100mg PO q24hours (600mg/ 24hours)

†Being 200mg q12hours when given w/ Valproic acid, which ↑Lamotrigine levels >2fold
‡Correction of measured total plasma Phenytoin level for albumin:

\[
\text{Measured plasma Phenytoin level} = (0.2 \times \text{albumin level}) + 0.1
\]

Additional Phenytoin needed if subtherapeutic:
\[
(0.7 \times \text{wt in kg}) \times (\text{desired level} - \text{actual level})
\]
\[
0.92
\]

°90% of plasma Phenytoin is protein bound. In critical illness, protein synthesis & binding affinity are altered→
  • ↑Free, active Phenytoin, without any effect on the total plasma content, resulting in potential toxicity. Therefore, in critical illness, free levels should be monitored

Side effects: Withdrawal from anti-seizure medications should be done gradually in order to prevent rebound ↑seizure frequency &/or severity

Mucocutaneous
• Dermatitis, including Erythema multiforme, & its severe variants:
  ◦ Toxic epidermal necrolysis–TEN
  ◦ Stevens–Johnson syndrome–SJS

Carbamazepine specific screening:
• HLA–B*1502 genotyping in Asians, in whom:
  ◦ This allele occurs almost exclusively
  ◦ Carbamazepine mediated SJS occurs 10X relative to other ethnic groups
  ...being highly associated w/ ↑Carbamazepine mediated SJS risk

Musculoskeletal
• Hepatic enzyme inducing antiseizure medications (ex: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Topiramate) likely→
  ◦ Osteoporosis, w/ the recommendation of concurrent Vitamin D & calcium supplementation
Neurologic
• Altered mental status
• Double vision = diplopia
• Headache
• Incoordination = ataxia
• ↓Neuropathic pain
• Sedation

Maternofetal
• Teratogenic during the 1st trimester

Overdose:

Pulmonary
• Respiratory depression

Interactions:
• Hepatic enzyme inducing antiseizure medications (ex: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Topiramate) → ↑hepatic clearance of:
  ◦ Antiretroviral medications
  ◦ Chemotherapeutic medications
  ◦ Immunosuppressive medications (ex: glucocorticoids, Cyclosporine)
  ◦ Oral contraceptive pills. Therefore, ♀'s taking these medications should use preparations containing ≥ 50μg of ethinyl estradiol to ↓ pregnancy risk
• Oral contraceptive pills →
  ◦ ↑Clearance of Lamotrigine, w/ levels being transiently ↑ if the contraceptive includes a week of inactive tablets

Carbamazepine specific:

General
• Fever
• ↑Weight

Cardiovascular
• Heart block

Gastrointestinal
• Diarrhea
• Nausea ± vomiting
• Hepatitis

Neurologic
• Aseptic meningitis
Hematologic
• Agranulocytosis (1/200,000)
• Aplastic anemia (1/500,000)
• Benign leukopenia
• Hyponatremia
  • Pseudolymphoma: A benign lymphocytic skin infiltrate that mimics cutaneous lymphoma, usually resolving within several months after discontinuation
  • Thrombocytopenia, w/ ↑doses

Clonazepam specific:
• Hypersalivation

Ethosuxamide specific:
  Gastrointestinal
    • Diarrhea
    • Nausea ± vomiting
  Hematologic
    • Blood dyscrasias

Lamotrigine specific:
  Gastrointestinal
    • Hepatitis

Levetiracetam specific:
  Neurologic
    • Psychosis–rare

Oxcarbazepine specific:
  Hematologic
    • Hyponatremia

Phenytoin specific:
  General
    • Fever
    • Lymphadenopathy
  Autoimmune
    • Systemic lupus erythematos–SLE like syndrome
  Cardiovascular
    • Heart block
Gastrointestinal
• Hepatic granulomas
• Hepatitis

Mucocutaneous
• Coarse facial features, termed leonine facies, characterized by thickening of the subcutaneous tissue about the eyes & nose
• Gingival hyperplasia—30%
  ◦ Once established, may only partially regress
• Hirsutism (5% overall, 30% of young ♀)

Musculoskeletal
• Vitamin D inactivation
  ◦ Osteoporosis

Neurologic
• Nystagmus
• Polyneuropathy

Hematologic
• Hypocalcemia
• Hyperkalemia
• Megaloblastic anemia
• Pseudolymphoma: A benign lymphocytic skin infiltrate that mimics cutaneous lymphoma, usually resolving within several months after discontinuation

Maternofetal
• Teratogenic
  ◦ Fetal hydantoin syndrome, characterized by:
    –↓ Growth → ↓ birth weight
    – Congenital physical anomalies, including cardiac defects & craniofacial deformities characterized by microcephaly, cleft lip &/or palate, broad nasal bridge, hypertelorism (wide set eyes), & epicanthal folds (skin fold of the upper eyelid, overlapping the nasal portion of the eye)
    –↓ Development
    – Cognitive impairment

Topiramate specific:

General
• Heat stroke: ↑ Core body (rectal) temperature, usually being ≥ 107.6°F = 42°C, being termed hyperthermia
  ◦ Systemic enzymatic dysfunction → cell dysfunction & death
• ↓ Weight
Genitourinary
• Nephrolithiasis–1.5%

Ophthalmologic
• Acute = narrow = closed (iridocorneal) angle glaucoma–rare, being a MEDICAL EMERGENCY, as blindess may occur within hours to days (usually @ ≤ 1 month)

Hematologic
• Metabolic acidemia–3%

Valproic acid specific:
General
• ↑Weight

Gastrointestinal
• Diarrhea
• Nausea ± vomiting
• Hepatitis–rare
• Pancreatitis–rare

Genitourinary
• Altered menstrual hemorrhage, being either ↑ or ↓
• Polycystic ovary syndrome

Mucocutaneous
• Alopecia
• Hirsutism

Neurologic
• Secondary Parkinson’s disease, w/ effects being reversible after discontinuation
• Tremor

Hematologic
• ↑Ammonia levels
• Thrombocytopenia

Maternofetal
• ↑Relative risk of cognitive deficits in children exposed in utero (relative to other antiseizure medications), being dose dependent

Zonisamide specific:
General
• Heat stroke: ↑Core body (rectal) temperature, usually being ≥ 107.6°F = 42°C, being termed hyperthermia→
  ◦ Systemic enzymatic dysfunction→cell dysfunction & death
• Weight

Genitourinary
• Nephrolithiasis – 2%

Hematologic
• Aplastic anemia

**Monitoring:**

• Plasma medication levels should be checked @:
  ◦ Baseline, after initiating treatment, & until therapeutic levels are reached & sustained
  ◦ Addition of a potential interacting medication
  ◦ Change in gastrointestinal, hepatic, or renal function
  ◦ Occurrence of side effects
  ◦ Pregnancy, which ↑ the clearance of many antiseizure medications (esp. Lamotrigine)

---

**TREATMENT OF ACTIVE SEIZURE**

• Place the patient on a monitor

• Place an oral airway, if possible, w/ 100% O₂ via a non-re-breather mask

• Draw a finger blood glucose

• Establish an IV line & draw blood for:
  ◦ Complete blood count
  ◦ Chemistry
  ◦ Arterial blood gases
  ◦ Coagulation studies
  ◦ Toxicology screen (including ethanol level)
  ◦ Medication levels
  ◦ Other possible etiologic tests

• **Intravenous empiric treatment**
  ◦ 50mL of a 50% dextrose solution IV
  ◦ Naloxone 2mg IV
  ◦ Thiamine (vitamin B1) 100mg IV. Patients should receive Thiamine either before or w/ the first glucose solution, in order to prevent glucose mediated Thiamine reserve depletion in alcoholics (or other nutritionally deficient patients) → either:
– Wernicke’s encephalopathy
– Korsakoff’s syndrome

**Magnesium sulfate IV, if eclampsia is suspected**
– 4–6g IV infusion over 20 minutes, repeated for recurrent seizures, then 2g/hour IV infusion to be continued for ≥ 24 hours postpartum

**Pyridoxine (vitamin B6), if Isoniazid–INH overdose is suspected**
– 5g IV over 5 minutes (also prn recurrent seizure activity), as overdose mediated seizures are resistant to the usual antiseizure treatment. If needed, Pyridoxine can be given as a slurry using crushed tablets in the same dose

• **Treat the etiologic cause** if known

• **Seizure precautions**
  o Padded bed rails

• **If unconscious, place in the left lateral decubitus position**
  o ↓ Aspiration risk

---

### BENZODIAZEPINES

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorazepam (Ativan)</strong></td>
<td><strong>LK/ U: 4mg IM/ IV slow push q5minutes prn</strong></td>
</tr>
</tbody>
</table>

**Mechanism:**
• Bind to a benzodiazepine receptor site on the neuronal inhibitory gamma aminobutyric acid–GABA_A chloride ion channel →
  o ↑ **Frequency** of channel opening in the concomitant presence of GABA →
    – Neuronal inhibition

**Outcomes:**
• **Seizure termination within 5 minutes in 80% of cases**

**Side effects:**

- Cardiovascular
  • Hypotension

- Gastrointestinal
  • Nausea ± vomiting
Neurologic
- Altered mental status
- Incoordination = ataxia
- Double vision = diplopia
- Headache
- Sedation
- Physical & psychological dependence
- Tolerance
- Additive central nervous system depression effects in combination w/:
  - Antihistamine medications
  - Ethanol
  - Sedative/ hypnotic medications
    - Barbiturates
    - Buspirone
    - Cyclic ethers
    - Meprobamate
    - Zolpidem

Overdose:
- Pulmonary
  - Respiratory depression

SECOND LINE

<table>
<thead>
<tr>
<th>HYDANTOINS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (Trade)</strong></td>
</tr>
<tr>
<td>Phenytoin (Dilan-tin)</td>
</tr>
<tr>
<td>Fosphenytoin‡ (Cerebyx)</td>
</tr>
</tbody>
</table>

...followed by Phenytoin @ 100mg PO/ IV q8–6hours

†In order to ↓cardiovascular depression risk
‡A phosphorylated prodrug of Phenytoin, requiring 15minutes for conversion, thereby not achieving therapeutic levels any faster, but rather, being relatively safer than Phenytoin by avoiding possible Propylene glycol toxicity & Purple glove syndrome
Outcomes:

- The combination of a benzodiazepine & a hydantoin will terminate seizure activity in 90% of cases

Side effects:

**Cardiovascular**
- Atrioventricular block
- Hypotension

**Mucocutaneous**
- Pruritus (Fosphenytoin–50% > > Phenytoin–5%)

**Neurologic**
- Altered mental status
- Double vision = diplopia
- Headache
- Incoordination = ataxia
- ↓ Neuropathic pain
- Sedation

**Maternofetal**
- Teratogenic during the 1st trimester

Overdose:

**Pulmonary**
- Respiratory depression

**IV Phenytoin specific:**

**Cardiovascular**
- Progressive distal limb edema, erythema, pain, & cyanosis, termed ‘Purple glove syndrome’–6%, usually occurring within 24 hours of peripheral administration of the highly alkaline solution, requiring vascular surgery consultation, as it may →
  - Ischemia &/or compartment syndrome →
    - Necrosis, which both begins, & last heals around the intravenous site, w/ resolution perhaps requiring weeks–months

**Hematologic**
- Unlike Fosphenytoin, Phenytoin does not readily dissolve in aqueous solutions, requiring a nonpolar solvent such as propylene glycol (a colorless, odorless fluid) is required to keep the medication in solution, & can accumulate →
  - Propylene glycol toxicity →
    - Acute tubular necrosis → renal failure
- Altered mental status
- Anion gap metabolic acidemia
- Dysrhythmias
- Hemolysis
- Hyperosmolarity
- Seizures

...→↑plasma levels & **osmolar gap**. Being that propylene glycol is metabolized equally by the kidneys & liver, patients w/ renal or hepatic failure are @ ↑risk

**Fosphenytoin specific:**

**Hematologic**

- Hyperphosphatemia in patients w/ severe renal failure

**Contraindications:**

- ≥ 2nd degree heart block

---

**OR**

**BENZODIAZEPINES**

**Indications:**

- Contraindication to Hydantoin treatment

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Diazepam</strong> (Valium)</td>
<td>LK/ U: 10–20mg/ hour IV infusion</td>
</tr>
</tbody>
</table>

**THIRD LINE**

**Indications:**

- Seizure refractory to the above treatments–10% of patients

- **Endotracheal intubation**

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**BARBITURATES**

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenobarbital</strong> (Luminal)</td>
<td>L/ U: 20mg/ kg IV @ 50mg/ minute (usually being ~1–1.5g total over 20–30minutes respectively), then 5mg/ kg IV q15min-</td>
</tr>
<tr>
<td><strong>Mechanism:</strong></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>• Bind to a benzodiazepine receptor site on the neuronal inhibitory gamma aminobutyric acid–GABA&lt;sub&gt;A&lt;/sub&gt; chloride ion channel →</td>
<td></td>
</tr>
<tr>
<td>◦ <strong>Duration</strong> of channel opening in the concomitant presence of GABA →</td>
<td></td>
</tr>
<tr>
<td>– Neuronal inhibition</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Outcomes:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Seizure termination in 50% of refractory patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Side effects:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>• Hypotension</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>• Nausea ± vomiting</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
</tr>
<tr>
<td>• Altered mental status</td>
</tr>
<tr>
<td>• Incoordination = ataxia</td>
</tr>
<tr>
<td>• Double vision = diplopia</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Sedation</td>
</tr>
<tr>
<td>• Physical &amp; psychological dependence</td>
</tr>
<tr>
<td>• Tolerance</td>
</tr>
<tr>
<td>• Additive central nervous system depression effects in combination w/:</td>
</tr>
<tr>
<td>◦ Antihistamine medications</td>
</tr>
<tr>
<td>◦ Ethanol</td>
</tr>
<tr>
<td>◦ Sedative hypnotic medications</td>
</tr>
<tr>
<td>– Benzodiazepines</td>
</tr>
<tr>
<td>– Buspirone</td>
</tr>
<tr>
<td>– Cyclic ethers</td>
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<tr>
<td>– Meprobamate</td>
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<tr>
<td>– Zolpidem</td>
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</tbody>
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<thead>
<tr>
<th><strong>Overdose:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>• Respiratory depression</td>
</tr>
</tbody>
</table>
FOURTH LINE
Indications:
• Seizure refractory to the above treatments–5% of patients

<table>
<thead>
<tr>
<th>COMA INDUCING MEDICATIONS</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (Trade)</strong></td>
<td><strong>Pentobarbitol (Nembutal)</strong></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>LK/ U: 10–15mg/kg IV infusion over 1–2hours, then 1–1.5mg/kg/hour infusion</td>
</tr>
<tr>
<td><strong>Inhalational anesthesia</strong></td>
<td></td>
</tr>
</tbody>
</table>