Epilepsy

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Incidence, Prevalence, and Epidemiology

- Approximately **10% of the population** will experience a seizure at some time in their life.
- Up to **30% of all seizures** are provoked by **central nervous system (CNS) disorders** or insults (e.g., meningitis, trauma, tumors, and exposure to toxins); these seizures may become recurrent and require chronic treatment with AEDs.
- **Reversible conditions** such as **alcohol withdrawal, fever, and metabolic disturbances** may provoke acute, isolated seizures.
- Approximately **1%** of the general population has **epilepsy**

Terminology, Classification, and Diagnosis

- Epilepsy is a “disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequence of this condition”.

- By definition, epilepsy requires the occurrence of two or more seizures that are not acutely provoked by other illnesses or conditions.

Terminology, Classification, and Diagnosis

- A commonly used classification scheme for epileptic seizures:
- **Partial Seizure (Focal):** Simple & Complex, Partial Seizures That Evolve to Generalized Seizures
- **Generalized Seizures (Convulsive or Nonconvulsive):**
- **Myoclonic Seizures**
- **Clonic Seizures**
- **Tonic Seizures**
- **Tonic–Clonic Seizures**
- **Absence seizures**
- **Atonic (Astatic or Akinetic) Seizures**

Partial Seizures

- Simple partial (**focal motor or sensory**) seizures are localized in a single cerebral hemisphere or portion of a hemisphere.
- Consciousness **is not impaired during these** events.
- Various motor, sensory, or psychic manifestations may occur depending on the area of the brain that is affected.
- A single part of the body may twitch, or the patient may experience only an unusual sensory experience.

Partial Seizures

- Complex partial seizures result from the spread of focal discharges to involve a larger area.
- Consciousness is impaired and patients may exhibit complex but inappropriate behavior (**automatisms**) such as **lip smacking, picking at clothing, or aimless wandering.**
- A period of brief postictal lethargy or confusion is common.

Seizure Types

Generalized tonic–clonic seizures

- They are common. The patient **loses consciousness** and **falls** at the **onset**. Simultaneously, tonic muscle spasms begin and may be accompanied by a cry that results from air being forced through the larynx.
- **Bilateral**, **repetitive clonic movements** follow.
- After the clonic phase, patients **return to consciousness** but remain **lethargic** and may be **confused** for varying periods of time (**postictal state**)

- Urinary incontinence and tongue biting is common.
- It can be divided to **primary or secondary** type (Aura at onset of seizure)

Absence seizures

- occur primarily in children and often **remit during puberty**; affected patients may exhibit a **second type of seizure**.
- Absence seizures consist of a **brief loss of consciousness**, usually **lasting several seconds**.
- Simple (typical) absence seizures are **not** accompanied by **motor symptoms; automatisms, muscle twitching, myoclonic jerking, or autonomic manifestations** may accompany atypical (complex) absence seizures.
- Although consciousness is lost, **muscle tone is maintained** and patients do **not fall during absence seizures.**
- Patients are unaware of their surroundings and will have no recall of events during the seizure. Consciousness returns immediately when the seizure ends, and **postictal confusion does not occur.**

Treatment

- **Early control of epileptic** seizures is important because it allows normalization of patients' lives and **prevents** acute physical harm and long-term morbidity associated with recurrent seizures.

- **Pharmacotherapy** is the mainstay of treatment for epilepsy.
- The experts recommended **monotherapy** first, followed by a second monotherapy agent if the first failed.
- If the second monotherapy failed, the experts were not in agreement on whether to try a **third monotherapy** agent or to **combine two therapies**.

Antiepileptic Drugs (AEDs) Useful for Various Seizure Types

Primary Generalized Tonic–Clonic	Secondarily Generalized Tonic–Clonic	Simple or Complex Partial (Focal)	Absence	Myoclonic, Atonic/Akinetic
Most Effective With Least Toxicity[a]				
Valproate	Carbamazepine	Carbamazepine	Ethosuximide	Valproate
Levetiracetam	Oxcarbazepine	Oxcarbazepine	Valproate	Clonazepam
Lamotrigine	Levetiracetam	Levetiracetam	Lamotrigine	Rufinamide (Lennox–Gastaut Syndrome)

Overview of treatment

- In general, the goal of AED treatment is administration of sufficient medication to completely prevent seizures without producing significant toxicity.
- Frequent, “routine” determinations of serum AED concentrations are costly and not warranted for patients whose clinical status is stable.
- the results of individual serum concentration determinations must be evaluated carefully to decide whether a significant, clinically meaningful change has occurred.

Duration of Therapy

- A diagnosis of epilepsy may not necessitate lifelong drug therapy.

- AED therapy may be successfully withdrawn from some patients after a seizure-free period of 2 to 5 years.
- Therefore, many patients whose epilepsy is completely controlled with medication can stop therapy after a seizure-free period of at least 2 years.

- Withdrawal of each AED for at least 6 weeks would seem to be a safe approach. Gradual withdrawal is recommended even for medications such as phenobarbital that have long half-lives and should theoretically be “self-tapering.”

Risk Factors Possibly Predicting Seizure Recurrence After Antiepileptic Drug (AED) Withdrawal
<2 years seizure-free before withdrawal
Onset of seizures after age 12
History of atypical febrile seizures
Family history of seizures
2–6 years before seizures controlled
Large number of seizures (>30) before control or total of >100 seizures
Partial seizures (simple or complex)
Abnormal EEG persisting throughout treatment
Slowing on EEG before medication withdrawal
Organic neurologic disorder
Moderate to severe mental retardation

Carbamazepine Therapy

- Initiation of treatment with full therapeutic maintenance doses of carbamazepine often causes excessive side effects such as **nausea, vomiting, diplopia, and significant sedation.**

- Therefore, carbamazepine therapy should be initiated gradually and patients should be allowed time to acclimate to the effects of the drug.
- Final dosing requirements are difficult to anticipate in individual patients.
- A reasonable starting dosage of carbamazepine for A.R. would be **100 mg twice a day; her dosage could be increased by 100 to 200 mg/day every 7 to 14 days.**

Hematologic Toxicity

- Aplastic anemia and agranulocytosis have occurred in association with carbamazepine therapy.
- Several cases have been fatal; however, most cases occurred in older patients treated for trigeminal neuralgia.
- Leukopenia is relatively common in patients taking carbamazepine. It is usually mild and often reverses despite continued administration of the drug.
- Carbamazepine-associated hematologic disorders are **unrelated to drug dosage**; thus, these reactions appear to be **idiosyncratic**.

Hematologic Parameter Monitoring

- The likelihood of early detection of aplastic anemia or agranulocytosis through frequent blood counts is low, however, and such monitoring is costly.
- Because hematologic toxicity from carbamazepine primarily occurs early in therapy, a CBC should be obtained before therapy and at monthly intervals during the first 2 to 3 months of therapy;
- Thereafter, a yearly or every-other-year CBC, white blood cell count with differential, and platelet count should be sufficient

Hepatotixicity

- Hepatic adverse reactions are believed to be idiosyncratic or immunologically based.
- Aggressive laboratory monitoring of liver function tests (LFTs) probably is unnecessary.
- Alkaline phosphatase and γ-glutamyl-transferase concentrations often are elevated in patients taking carbamazepine (and other AEDs). This is believed to result from hepatic enzyme induction.

- **Baseline (pretreatment) determination of A.R.'s hepatic and hematologic status, possibly with monthly follow-up testing for 2 to 3 months, probably will be sufficient, thereafter** only every 1 to 2 years unless signs or symptoms of hepatic or hematologic disorders are observed

Autoinduction of Metabolism

- Carbamazepine is a potent inducer of hepatic cytochrome P-450 (CYP3A4).
- The drug is also a substrate for this enzyme. As a result, carbamazepine not only stimulates the metabolism of other CYP3A4 substrates but also induces its own metabolism by auto-induction.
- Carbamazepine's half-life after single acute doses is approximately 35 hours; with chronic dosing, its half-life decreases to 15 to 25 hours.
- Approximately 1 month may be required for the auto-induction process to reach completion after each increase in carbamazepine dose

Therapeutic Regimen

- Initial 200 mg BID (adults) or 100 mg BID (children) and weekly until therapeutic response or target serum concentrations.

- Usual maintenance doses 7–15 mg/kg/day in adults; 10–40 mg/kg/day in children

Lamotrigine Therapy

- An initial dosage of 50 mg/day given at bedtime is recommended; the daily dose can be increased by 50 mg every 1 to 2 weeks.
- Because R.H. is currently receiving carbamazepine, induction of liver enzymes is likely to increase her dosage requirements for lamotrigine.
- **Slow, gradual titration of dose may reduce risk of skin rash. Estrogen increases clearance.**
- A patient's ability to tolerate this medication ultimately determines dosage limitations.
- Onset of side effects (e.g., **nausea, diplopia, ataxia, and dizziness) may prevent further dosage increases.**

Lamotrigine Therapy

- **When added to enzyme inducers alone:**
- Initiate at 50 mg daily HS or 50 mg BID. Daily dose can be ↑ by 50–100 mg every 7–14 days. Usual maintenance doses of 400–500 mg/day. BID dosing may be necessary with enzyme inducer cotherapy.
- **When added to valproate alone:**
- Initiate at 25 mg QOD HS. Daily dose can be ↑ by 25 mg every 14 days. Usual maintenance doses of 100–200 mg/day.
- For patients **not taking valproate or an enzyme inducer**: Initiate at 25 mg QD HS. Daily dose can be ↑ by 25 mg every 14 days. Usual daily doses of 225–375 mg/day

Levetiracetam Therapy

- Levetiracetam should be initiated at a dosage of 250 to 500 mg 2 times daily.
- Although the manufacturer recommends initiating treatment at 500 mg twice daily, patients may better tolerate lower initial doses and more gradual titration.
- daily levetiracetam dose can be increased by 500 to 1,000 mg every 2 or 3 weeks, according to her tolerance of side effects and her change in seizure frequency.
- Although the drug reaches steady state quickly, allowing at least 2 weeks for observation before dosage increases may improve patient tolerability

Levetiracetam Therapy

- Somnolence, dizziness, asthenia are commonly reported. Behavioral symptoms (agitation, emotional lability, hostility, depression, and depersonalization) reported.

No hepatic (CYP450 or UGT) metabolism. 66% excreted unchanged in urine. Less than 10% protein bound. No significant drug interactions reported

Renal failure

patients with renal failure on dialysis, a dose of 500-1000 mg once daily is recommended, with a supplemental dose of 250-500 mg after dialysis treatment

Levetiracetam dosing in patients with renal impairement

Renal function	Creatinine clearance (ml/min/1.73 m^2)	Dosage administered BID
Normal	>80	500–1500
Mild	50–80	500–1000
Moderate	30–50	250–750
Severe	<30	250–500

Phenytoin therapy

- Patients should be informed that he may experience initial mild sedation from phenytoin.
- They should be cautioned that symptoms such as blurred or double vision, dysarthria, dizziness, or staggering may indicate that his dosage is too high; he should be instructed to notify his physician, pharmacist, or other health care professional.
- long-term use of phenytoin (as well as other AEDs) is associated with an increased risk of bone mineral loss and that this adverse effect warrants monitoring periodically

Safety concerns

- Phenytoin exhibits dose-dependent (Michaelis–Menten or capacity-limited) pharmacokinetics.

- Gum hyperplasia related to phenytoin is common and troublesome. Prevalence is estimated at 40% to 50% of treated patients.
- occurrence and severity of hyperplasia are related to the dose and serum concentration of phenytoin.

- Phenytoin may stimulate gingival mast cells to release heparin and other mediators that may encourage synthesis of excessive amounts of new connective tissue by fibroblasts.

Safety concerns

- Treatment of existing hyperplasia:

  (a) Dosage reduction or replacement of phenytoin with an alternative AED, if possible,

  (b) Surgical gingivectomy,

  (c) Periodontal treatment,

Safety concerns

- Nystagmus, ataxia, sedation may limit dosage. Gum hyperplasia, hirsutism common. Long-term use may cause osteomalacia.
- Peripheral neuropathy, hypersensitivity with liver damage rare. Possible increased risk of Stevens– Johnson syndrome/toxic epidermal necrolysis in Asian patients positive for HLA-B*1502.
- IM administration not recommended. Potential precipitation in IV solutions.

Dosing

- Initiate at maintenance dose of 4–5 mg/kg/day (300–400 mg/day). Titrate on basis of clinical response and target serum concentration.

- 3–4 weeks between dose ↑ recommended because of potentially slow accumulation.
- Therapeutic level: 10–20 mcg/mL/ Daily to BID (administration interval)

- Phenytoin suspension and chewable tablets contain free acid, whereas capsules contain sodium phenytoin.
- Therefore, phenytoin capsule products contain only 92% of the labeled content as phenytoin acid (i.e., a 100-mg sodium phenytoin capsule contains only 92 mg of phenytoin acid).

Antiepileptic Drug Impact on Bone

- Longer duration of AED therapy and exposure to multiple AEDs are thought to predict bone loss.
- Enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) have been associated with bone loss and an increased risk for fracture.
- Valproate, although not an enzyme inducer, is associated with decreased bone mineral density in children.

- Oral calcium and vitamin D supplementation should be implemented.

Hypersensitivity Reactions

- **Reactive arene oxide metabolites** of phenytoin (and other chemically similar AEDs) as possible causative agents for hypersensitivity reactions.
- Affected patients purportedly are predisposed **genetically** to the development of hypersensitivity, possibly because **a relative deficiency of epoxide hydrolase enzymes** allows the accumulation of **toxic concentrations of reactive epoxide metabolites**.
- **Carbamazepine, phenytoin, and phenobarbital** all are metabolized by similar pathways and converted to reactive arene oxides.
- It is hypothesized that **carbamazepine-induced liver damage** also may result from the effects of accumulation of reactive epoxide metabolites; these reactive metabolites differ from the 10,11-epoxide metabolite that accumulates during carbamazepine therapy.
- For this reason, these **drugs potentially cross-react in susceptible patients**.

Absence Seizures

- Ethosuximide, valproate, and lamotrigine are commonly used to treat absence epilepsy in the United States.
- Ethosuximide is a succinimide agent that blocks T-type calcium currents in the thalamus. The drug is effective against absence seizures, but is ineffective against other seizure types.
- Valproate, a carboxylic acid derivative with broad-spectrum activity against many focal-onset and generalized-onset seizure types, is highly effective but is associated with adverse effects (dose-related, non-dose-related, and severe idiosyncratic) that limits the drug's use among some patient groups.

Absence Seizures

- Most authorities now consider ethosuximide the drug of first choice for treatment of absence seizures.
- Valproate is more likely to cause significant **nausea and initial drowsiness and it is more likely to interact with other drugs, including AEDs.**
- Valproate usually is reserved for patients whose absence seizures **do not respond to ethosuximide.**
- Valproate was also **more efficacious than lamotrigine** for treatment of idiopathic generalized seizures (including absence) in the Standard and New Antiepileptic Drugs (SANAD) trial.
- **Clonazepam**, a benzodiazepine, often is effective for control of absence seizures.
- Therapy with this drug **is limited by prominent CNS side effects** (sedation, ataxia, and mood changes) and **development of tolerance to its antiepileptic effect after long-term use**

Ethosuximide (Zarontin)

Initial 20 mg/kg/day or 250 mg daily or BID; then ↑ by 250 mg/day every 2 weeks to therapeutic effect or target serum concentration

GI upset and sedation common with large single dose, especially on initiation.

Daily divided doses may be necessary despite long half-life.

Leukopenia mild, transient) in up to 7%; serious hematologic toxicity extremely rare

Up to 50% of patients with absence may exhibit tonic–clonic seizures independent of ethosuximide.

Monitoring Parameters

- Patient or caregiver education regarding **signs and symptoms associated with leukopenia** and **pancytopenia** (**e.g., sudden onset of severe sore throat with oral lesions, easy bruisability, increased bleeding tendency**) and instructions to consult the physician if these symptoms occur may be more important than laboratory monitoring.

Valproate Therapy

- Initial 5–10 mg/kg/day (sprinkle caps or syrup); then ↑ by 5–10 mg/kg/day weekly to therapeutic effect or target serum concentration.

- Manufacturer's recommended usual **maximal dose of 60 mg/kg/day** often must be exceeded clinically (especially for patients receiving enzyme-inducing AED) to achieve optimal clinical results.

- Daily dosing recommended for ER product; **doses should be 8%–20% higher than non-ER products**

Safety concerns

- **GI upset, hair loss, appetite stimulation, and weight gain common**.
- **Dose-related tremor and thrombocytopenia** may occur.
- Serious **hepatotoxicity** extremely **rare with monotherapy** and in patients younger than 2 years of age.
- Alopecia occurs in 0.5% to 12% of patients and may improve **with dose reduction &** use of mineral supplements (zinc)

- **Enteric-coated tablets or capsules or ER tablets may ↓ GI toxicity.**
- Time to peak serum concentrations delayed for 3–8 hours with enteric coating; longer delay if given with food; serum concentrations must be interpreted carefully.

Monitoring parameters

- Once VPA therapy is initiated, **liver function tests, VPA serum levels, and CBCs with differential and platelets** should be monitored **at least monthly for the first 3 months** and **every 3 to 6 months thereafter.**
- Body weight should also be determined at baseline and monitored monthly during therapy.
- VPA-induced thrombocytopenia occurs in 18% of patients and is associated with female gender and higher VPA levels (>100 mcg/mL in women and >130 mcg/mL in men).
- In most patients, thrombocytopenia is asymptomatic and responds to a lowering of the VPA dosage; complete discontinuation of the drug is usually unnecessary

Dosage forms

Febrile Seizures

- Up to 8% of children have a febrile seizure between 6 months and 6 years of age.
- Simple febrile seizures occur with a fever of **greater than or equal to 38°C** in previously normal children younger than 5 years of age. They last **less than 15 minutes** and **have no focal features.**
- The associated seizure does not arise from CNS pathology.
- **Complex febrile seizures** show **focal characteristics or are prolonged longer than 15** minutes. The child may or may not have previous neurologic abnormalities.
- The risk of occurrence of unprovoked afebrile seizures after a febrile seizure is 4 times greater than in the general population.

Febrile Seizures

- If the patient is not having a seizure at present, AED therapy is not required.
- Measures to reduce her elevated temperature should be initiated; however, these measures may not reduce the risk of further seizures. Acetaminophen and tepid sponge baths usually are helpful.
- If patients experience prolonged or repeated febrile seizures, either **diazepam** or, less commonly, midazolam may be administered. **Rectal diazepam gel** can be used for this purpose.
- Long-term treatment or prophylaxis with AED for simple febrile seizures is not recommended

Febrile Seizures

- **AED prophylaxis for febrile seizures** is probably **not warranted** for J.J., even though she is at risk for both development of epilepsy and recurrence of febrile seizures.
- **No evidence supports that medication will significantly affect her later development of epilepsy.**
- Although **antipyretic measures** (tepid sponge baths, **acetaminophen or ibuprofen**) are of questionable benefit, they can be considered at the onset of fever because these interventions are usually safe and well tolerated.
- Many febrile seizures occur early in the course of an illness before fever is detected; nevertheless, vigilance by her parents **and early antipyretic therapy may help prevent further febrile seizures.**

Febrile Seizures

- Acetaminophen is the most common antipyretic agent used in children. The usual dose, oral or rectal, is 10 to 15 mg/kg/dose administered every 4 to 6 hours as needed to a maximum of 75 mg/kg/day.

- Ibuprofen is administered as 5 to 10 mg/kg/dose orally every 6 to 8 hours as needed to a maximum of 40 mg/kg/day.

Pregnancy and lactation

- For women of childbearing potential, prepregnancy planning and counseling are important.
- **Pre-pregnancy counseling** also should include the importance of at least 0.4 mg/day of folic acid supplementation and medication adherence.
- **Monotherapy** is preferred whenever possible, because the relative risk of birth defects & improve patient compliance.
- The AED should be given **at the lowest effective dose** to reduce the possibility of birth defects.
- **Gradual discontinuation of AED before pregnancy** may be considered if a woman has been seizure-free for 2 years or longer

Oral Contraceptive Interaction

- Phenobarbital, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, perampanel, and felbamate have been shown to **increase the metabolism of ethinylestradiol and progestogens.**

- This effect is not associated with valproate, lamotrigine, gabapentin, tiagabine, zonisamide, levetiracetam, lacosamide, or pregabalin.
- **Topiramate** in polytherapy and **at high dosages** (200–800 mg/day) appears to have a mild, though measurable, effect.

- The estrogen component in oral contraceptives increases the clearance of lamotrigine. **Lamotrigine** clearance may increase twofold when contraceptive steroids are begun and fall by 50% when contraceptive steroids are discontinued

Oral Contraceptive Interaction

1. A second contraceptive method (e.g., condoms, intrauterine devices, or spermicide) is recommended to avoid contraceptive failure.
2. Tubal ligation is also an alternative.
3. An additional alternative that could be considered is injectable depot medroxyprogesterone acetate. Although there is a lack of clinical studies substantiating its effectiveness in patients on enzyme-inducing AED

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Teratogenicity

- Most AEDs are believed to exert their teratogenic effects (and possibly other adverse effects such as hepatotoxicity) partly via reactive epoxide metabolites.

- The American College of Obstetricians and Gynecologists recommends **4 mg of folic acid daily for women at risk of having offspring with neural tube defects** (including women taking anti-seizure drugs).
- In addition to physical malformations, AED exposure in utero has an adverse effect on neurodevelopment.

- Women taking **carbamazepine, phenobarbital, primidone, or phenytoin** should receive **vitamin K 10 mg orally every day from 36 weeks of gestation until delivery**, and babies should also receive **vitamin K 1 mg IM at birth**

Lactation

- In a lactating woman who is taking medications, the risk of drug exposure to the infant needs to be weighed against the benefits of breast-feeding. All drugs transfer into milk to some extent.
- For most first-generation AEDs (carbamazepine, phenytoin, valproic acid), breast-feeding results in negligible AED plasma concentrations in the infants.
- For the newer AEDs, breast-feeding should be done cautiously and the infant should be monitored for excess AED plasma concentrations and toxicity, if possible.

Status epilepticus

- Status epilepticus (SE) is operationally defined as “either continuous seizures lasting at least 5 minutes or 2 or more discrete seizures between which there is incomplete recovery of consciousness.
- generalized convulsive SE; this is the most common type and it is associated with the greatest risk of systemic and neurologic damage.
- Vital signs (tachycardia, elevated blood pressure, increased respiratory rate, and elevated body temperature) are typical for a patient in SE.

General Treatment

- IV administration of rapid-acting anticonvulsant medication should begin as soon as possible to terminate seizure activity.

- Lorazepam, phenytoin, and fosphenytoin are the agents most commonly used as IV therapy in the initial treatment of SE.

Intermittent drug dosing in SE

Drug	Initial dosing	Administration rates and alternative dosing recommendations	Serious adverse effects	Considerations
Diazepam	0.15 mg/kg IV up to 10 mg per dose, may repeat in 5 min	Up to 5 mg/min (IVP) Peds: 2–5 years, 0.5 mg/kg (PR); 6–11 years, 0.3 mg/kg (PR); greater than 12 years, 0.2 mg/kg (PR)	Hypotension Respiratory depression	Rapid redistribution (short duration), active metabolite, IV contains propylene glycol
Lorazepam	0.1 mg/kg IV up to 4 mg per dose, may repeat in 5–10 min	Up to 2 mg/min (IVP)	Hypotension Respiratory depression	Dilute 1:1 with saline IV contains propylene glycol
Midazolam	0.2 mg/kg IM up to maximum of 10 mg	Peds: 10 mg IM (>40 kg); 5 mg IM (13–40 kg); 0.2 mg/kg (intranasal); 0.5 mg/kg (buccal)	Respiratory depression Hypotension	Active metabolite, renal elimination, rapid redistribution (short duration)
Fosphenytoin	20 mg PE/kg IV, may give additional 5 mg/kg	Up to 150 mg PE/min; may give additional dose 10 min after loading infusion Peds: up to 3 mg/kg/min	Hypotension Arrhythmias	Compatible in saline, dextrose, and lactated ringers solutions
Lacosamide	200–400 mg IV	200 mg IV over 15 min No pediatric dosing established	PR prolongation Hypotension	Minimal drug interactions Limited experience in treatment of SE
Levetiracetam	1,000–3,000 mg IV Peds: 20–60 mg/kg IV	2–5 mg/kg/min IV		Minimal drug interactions Not hepatically metabolized

Phenobarbital	20 mg/kg IV, may give an additional 5–10 mg/kg	50–100 mg/min IV, may give additional dose 10 min after loading infusion	Hypotension Respiratory depression	IV contains propylene glycol
Phenytoin	20 mg/kg IV, may give an additional 5–10 mg/kg	Up to 50 mg/min IV; may give additional dose 10 min after loading infusion Peds: up to 1 mg/kg/min	Arrhythmias Hypotension Purple glove syndrome	Only compatible in saline IV contains propylene glycol
Topiramate	200–400 mg NG/PO	300–1,600 mg/day orally (divided 2–4 times daily) No pediatric dosing established	Metabolic acidosis	No IV formulation available
Valproate sodium	20–40 mg/kg IV, may give an additional 20 mg/kg	3–6 mg/kg/min, may give additional dose 10 min after loading infusion Peds: 1.5–3 mg/kg/min	Hyperammonemia Pancreatitis Thrombocytopenia Hepatotoxicity	Use with caution in patients with traumatic head injury; may be a preferred agent in patients with glioblastoma multiforme

IM intramuscular; *IV* intravenous; *IVP* intravenous push; *min* minute; *NG* nasogastric; *PE* phenytoin equivalents; *PEDs* pediatric; *PO* by mouth; *PR* rectal administration; *PRIS* propofol related infusion syndrome

General Treatment

- IV phenytoin can be administered by direct injection into a running IV line.
- The rate of administration should be no faster than 50 mg/minute to minimize the risk of hypotension and acute cardiac arrhythmias. Cardiovascular status (blood pressure, electrocardiogram) should be monitored closely during administration.

Thank You!