Anticonvulsants

Mike Hodgman

- Currently ~ 24 approved medications for seizure management in US
- Many off label uses: neuropathic pain, headache/ migraine, mood disorders, PTSD, bulimia, addiction management, obesity, drug withdrawal….
- Some with abuse potential
- Significant issues with enzyme induction/ drug interactions with some

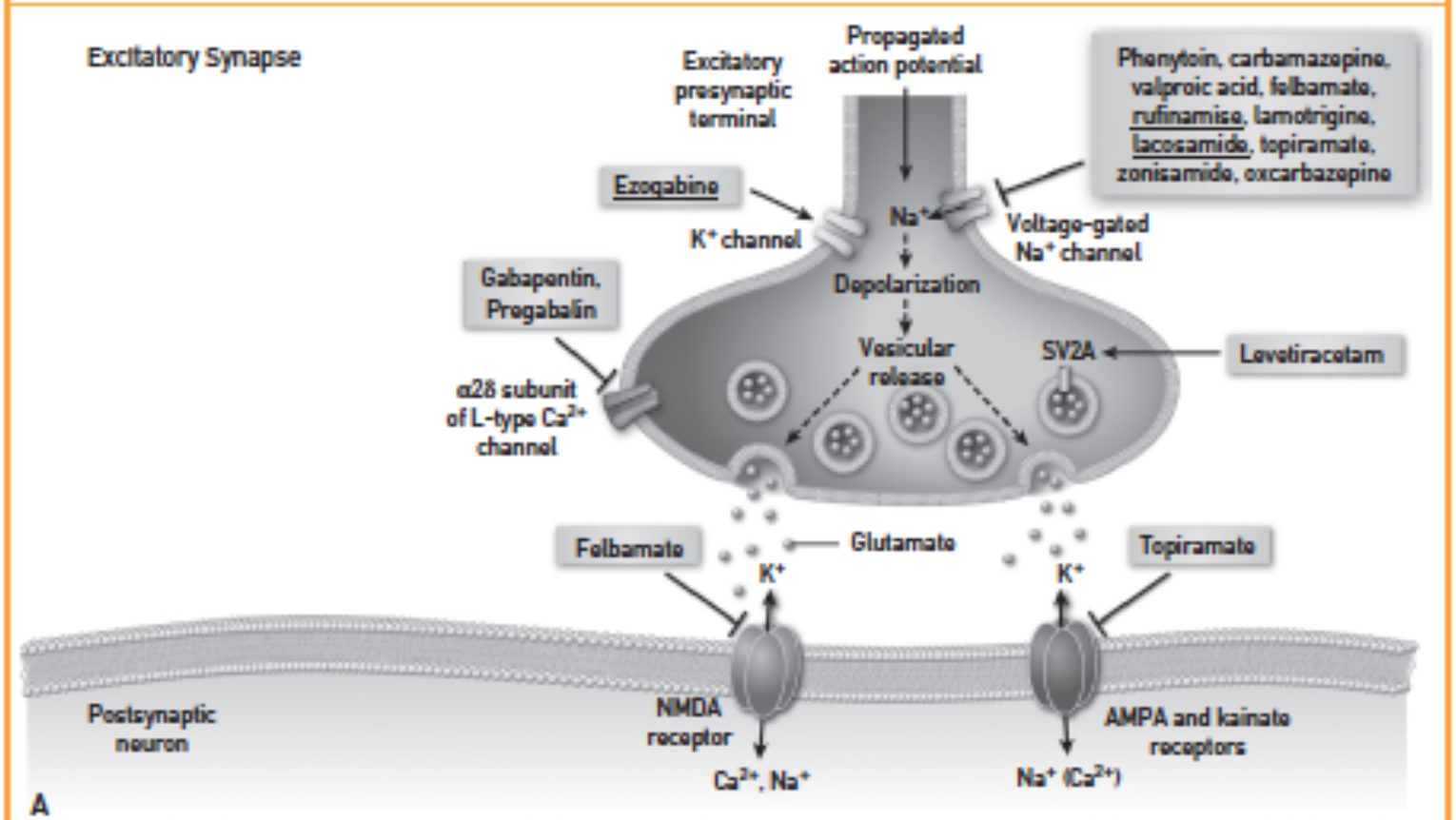


FIGURE 1. Figure and legend are modified and reprinted, with permission, from Bialer and White[1] and Rho.[2] Please see text for details. It is important to note that multiple mechanisms of action are ascribed to any given antiepileptic drug (AED). The diagram emphasizes the major mechanism of action for each AED. Part A shows drugs which may prevent seizures by acting upon excitatory synapses and Part B shows drugs which may affect inhibitory synapses. GABA = γ-aminobutyric acid; GABA-T = GABA transaminase; GAD = glutamic acid decarboxylase. Adapted from *Nat Rev Drug Discov*[1] and *Epilepsia*,[2] with permission.

Mayo Clin Proc. 2012;87:879-889

Modest goal

- review a few of more commonly used for seizure management
- general outline to approach patient who may be intoxicated with an anti-seizure medication
- anti-convulsant hypersensitivity syndrome (DRESS)
  - Drug Reaction with Eosinophlia and Systemic Symptoms

Questions

- With overdose:
  - What anti-convulsants may cause seizures?
  - What anti-convulsants may cause cardiac conduction disturbances?
- What anti-convulsants may lead to liver injury?
- When should we consider MDAC (multi-dose activated charcoal) or hemodialysis?

Gabapentin

- SAFE
- excessive dosing, overdose = sedation
    - may see myoclonic activity from disinhibition
- renally cleared:
    - accumulates if not dose adjusted

Gabapentin abuse

- Jail house drug
  - cocaine substitute by insufflation
- Insufflation gabapentin anecdotally reported to cause seizures
- Enhances effects methadone
  - although pregabalin better than gabapentin

Am J Addict 2004;13:321-323
Eur Addict Research 2014;20:115-118

Gabapentin toxicity

- management supportive
- is dialyzable but not really necessary for this alone (low mw, low Vd, no protein binding)

https://commons.wikimedia.org/wiki/File:Pregabalin.JPG

Pregabalin

- How is this different than gabapentin?
    - GI absorption is <u>much</u> more rapid, much greater bioavailability
        - sedation; but also, seizures
- Like gabapentin, nil metabolism with renal clearance
- Management of pregabalin overdose like gabapentin

Pregabalin abuse

- effect similar to ethanol,
  - Belfast, Ireland: “Budweiser’s”
- 6 of 10 patients seen in one Belfast ED following recreational abuse had seizures
  - insufflation or orally
  - dose 500- 1400 mg

Emerg Med J 2013;30:874

Withdrawal syndrome from abrupt cessation of either gabapentin or pregabalin

- disorientation, confusion, agitation, tachycardia, diaphoresis, tremor, and seizure

- benzodiazepine resistance to gabapentin withdrawal reported, with response to reinstitution of gabapentin

J Clin Psychiatry. 2007; 68:483–4

Phenytoin toxicity

- toxicity: cerebellum and vestibular systems
- ataxia, horizontal nystagmus
- higher concentrations: lethargy, confusion

Phenytoin

- Michaleis-Menton kinetics
  - really long half life with toxicity
  - CYP 2C9, 2C19 inhibitors may slow phenytoin metabolism…first order to zero order kinetics
- Na channel blocker (Vaughn Williams 1B)
  - no QRS widening
- Does phenytoin cause seizures at very toxic concentrations? Rare case reports with levels usually > 40 mcg/mL (I'm not convinced…)

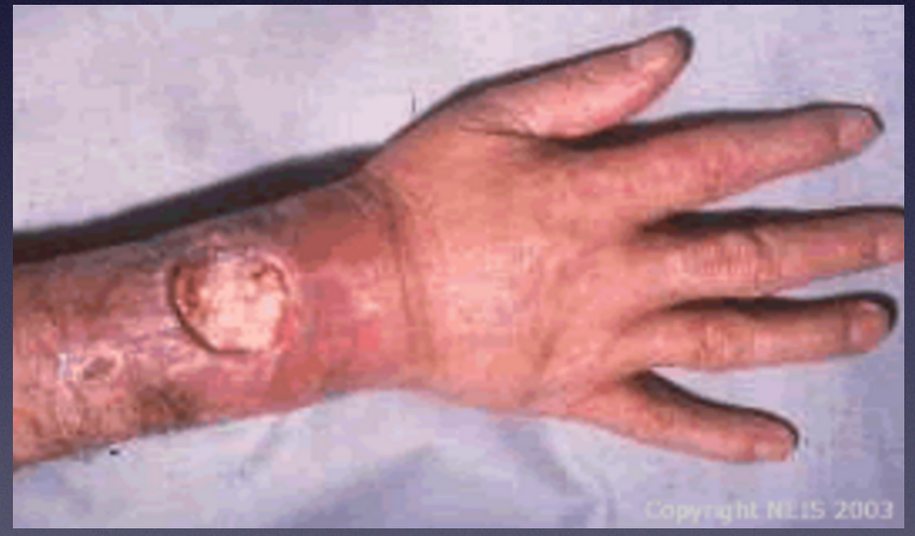
Singapore Med J 1999;40:276-7

Phenytoin toxicity

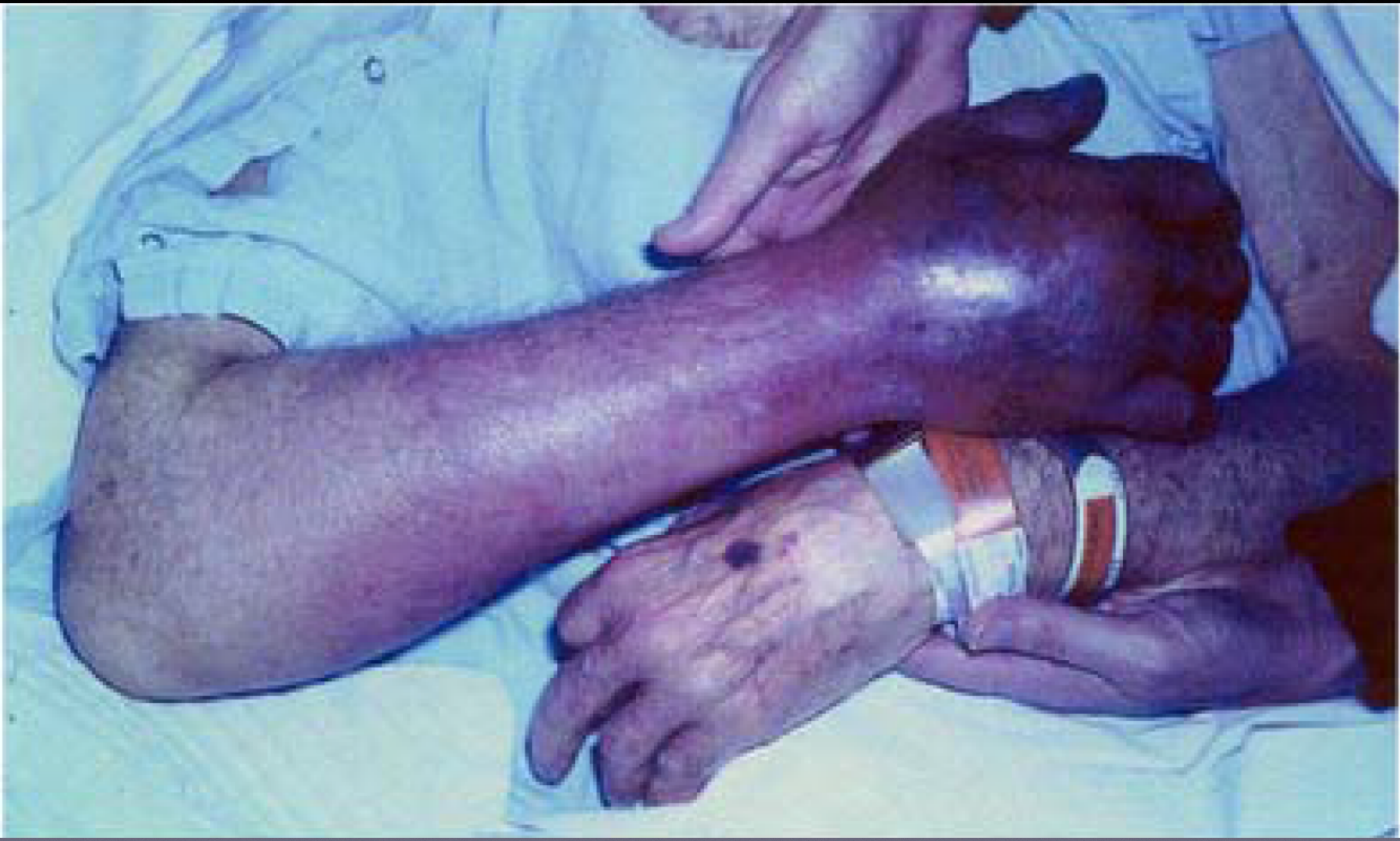
- Chronic toxicity: Stop the drug
  - If in a safe environment (and unintentional), not necessarily an admit
- Acute
  - activated charcoal
- MDAC will enhance clearance

Phenytoin use in ED

- Infusion rate
  - rapid infusions associated with hypotension
    - propylene glycol diluent
- Extravasation: caustic
- Purple glove syndrome
  - progressive swelling, discoloration extending distally, may or may not have obvious extravasation



http://www.iv-therapy.net/node/16



“I’m numb”

- 28 yo female presents with diffuse paresthesia and weakness.

“I’m numb”

- 28 yo female presents with diffuse paresthesia and weakness. She reports a diarrheal illness past several days, no vomiting.
- PH: migraine, medications: topiramate, prn triptan
- Exam: Alert, cooperative. BP 105/60 mm Hg, P 90 bpm, RR 22/min, afebrile. General exam unrevealing, no tremor or hyper-reflexia.

136	116	28
3.1	14	1.0

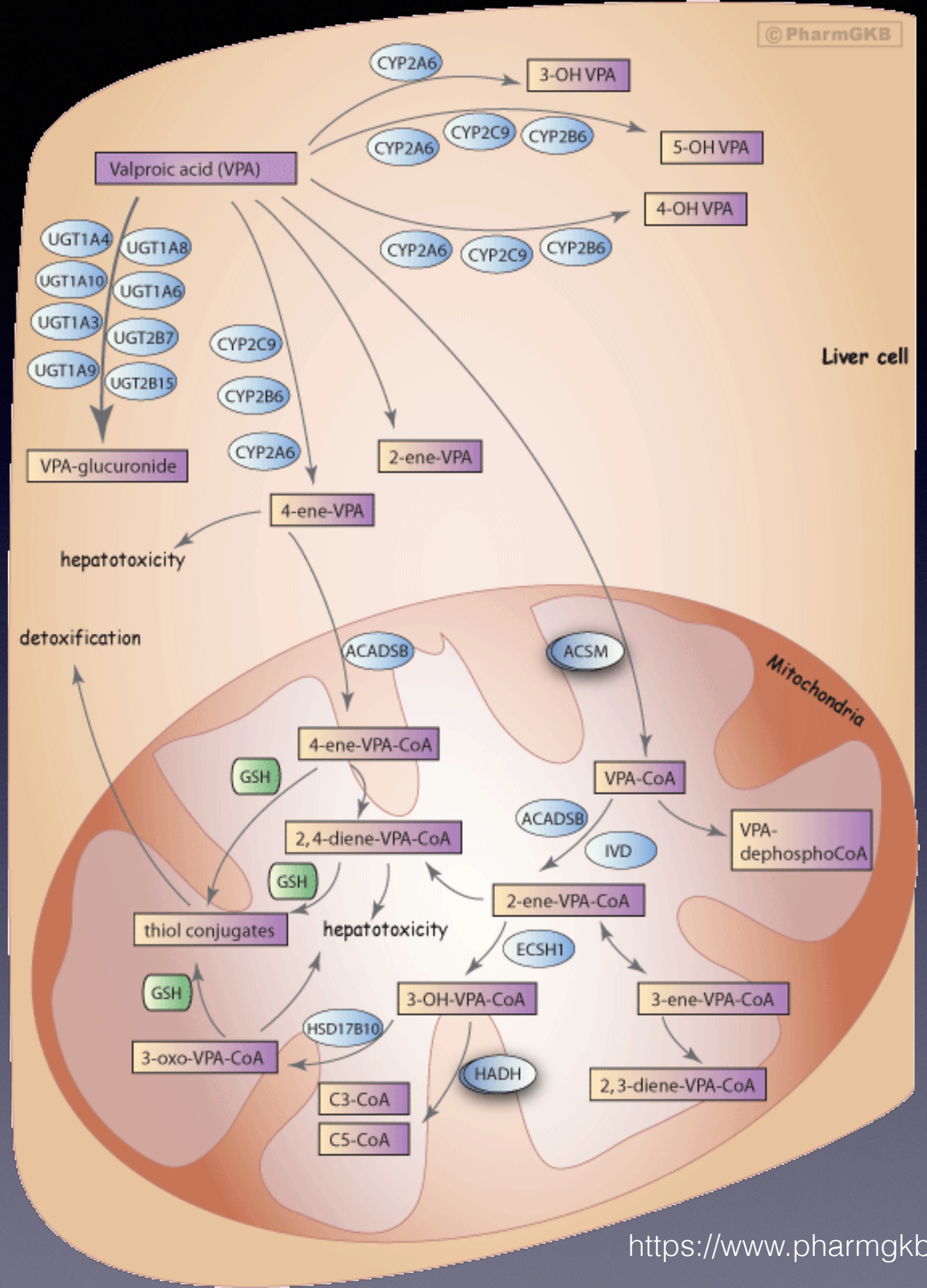
WBC 6.1
13.1/40.8%

Topiramate

- Weak carbonic anhydrase inhibitor
- May result in a modest non-gap hyperchloremic metabolic acidosis
  - common side effect: tingling
  - increased incidence renal stones
- In this case GI losses of bicarbonate likely aggravated non-gap acidosis

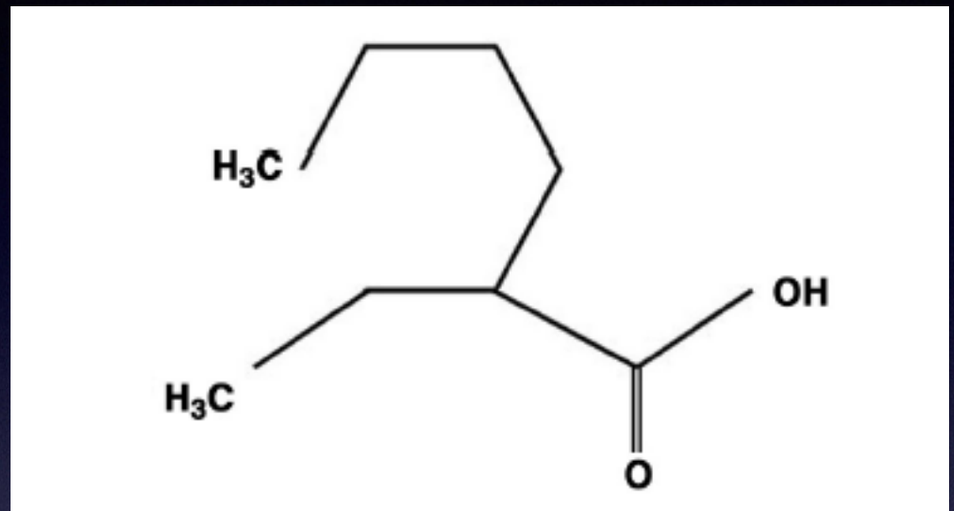
Topiramate

- acute toxicity
  - lethargy, hallucinations, myoclonus, seizures
- management
  - supportive



https://www.pharmgkb.org/pathway/PA165964265

Valproic acid, divalproex



- 2-n-propylpentoic acid
- hepatotoxin
- extensive hepatic metabolism
    - mitochondrial toxin: steatosis, acidosis
    - interference with urea synthesis: hyperammonemia
- L-carnitine depletion

Intrinsic hepatotoxin

- Risk is especially high in younger children, up to several years age
- and especially if on > 1 anti-seizure medication, ketogenic diet
- hyperammonemia, acidosis, transaminitis
- looks like Reye’s syndrome

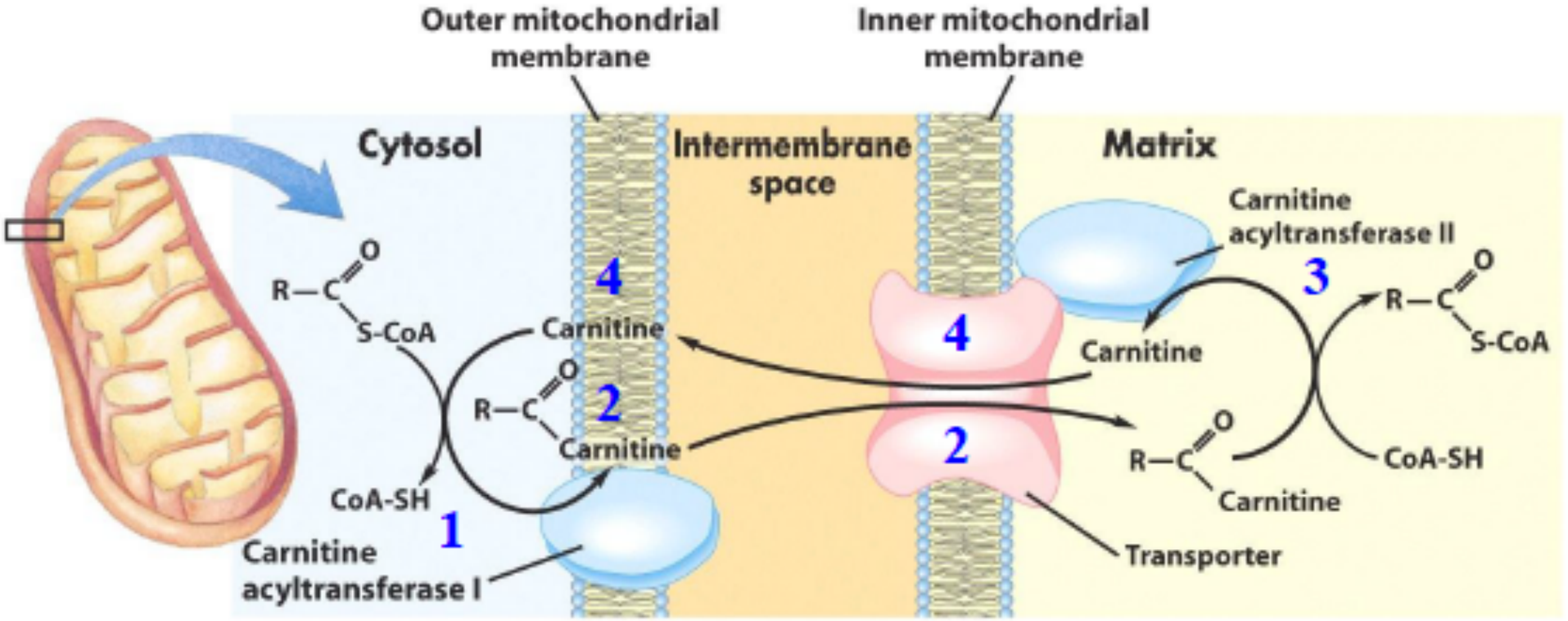
VPA acute Toxicity

- sedating, lethargy……..coma
  - >150 ug/mL…..200s….
- really bad: respiratory depression, hypotension, lactic acidosis, seizures, cerebral edema and death
  - typically north of 500-600 ug/mL
- other metabolic complications: hyperNa, hypoCa
- may see bone marrow suppression several days post large OD

VPA toxicity

- Lab studies should include
  - valproic acid concentration, electrolytes, liver tests, ammonia, lactic acid
- Supportive care for most
- Activated charcoal
  - consider MDAC if massive OD, ER formulation

FA - Carnitine Shuttle



https://www.studyblue.com/notes/note/n/fatty-acid-metabolism/deck/7312907

- Valproic acid depletes carnitine carnitine depletion impairs fatty acid metabolism
- Carnitine depletion increase production VPA metabolites that impair urea synthesis…..increased ammonia

Carnitine

- When should I give carnitine?
  - VPA associated coma, acidosis, hyperammonemia or hepatotoxicity
  - may be considered prophylactically after an acute overdose

Hemodialysis

- Small molecule, lower protein binding at very toxic concentrations, small Vd (0.1-0.4 L/kg)
- When should I consider hemodialysis?
  - refractory hypotension, profound coma, lactic acidosis, “severe” hyperammonemia
  - concentration based
    - EXTRIP: recommend > 1300 mg/dL, consider > 900 mg/dL

extrip-workgroup.org

- A 12 month old is brought to ED by EMS with coma and respiratory depression. EMS is bagging the child.
- Child drank older sibling’s medication earlier
- Unresponsive. BP 102/60 mm Hg, P 120s bpm, afebrile. Pupils reported reactive. Child withdraws to pain, extremities with “spasms”

- Older brother is on carbamazepine
- 100 mg/ 5 mL, up to 100 mL missing = 2 g
- usual ped dose 20-30 mg/kg/d
- estimated dose: up to 200 mg/kg

Carbamazepine

- Absorption solid formulation slow, peak levels 4+ h after ingestion, can be very delayed with overdose.
    - with elixir more rapid
- extensive hepatic metabolism, active metabolite (CBZ 10,11-epoxide) that undergoes enterohepatic recirculation
- Structurally similar to TCAs

Toxicity

- sedating, ataxia, dysarthria
- weakly anticholinergic
- hypertonicity, movement disturbances
- cardiac: sinus tachycardia, rarely conduction disturbances (QRS, QT), cardiac depressant at really toxic levels
- seizures at very toxic levels (> 40 mcg/mL)
- Na channel antagonism
- adenosine antagonism
- Metabolic: hyponatremia

Kids v adults, CBZ

- higher incidence movement disturbances
  - dystonia
  - choreoathetosis
- and seizures
- EKG changes less common

Carbamazepine

- half life about 10-20 hours with chronic use
- this drug also has Michaelis- Menton kinetics, although transition at more toxic levels than with phenytoin
- active metabolite undergoes enterohepatic recirculation

Laboratory

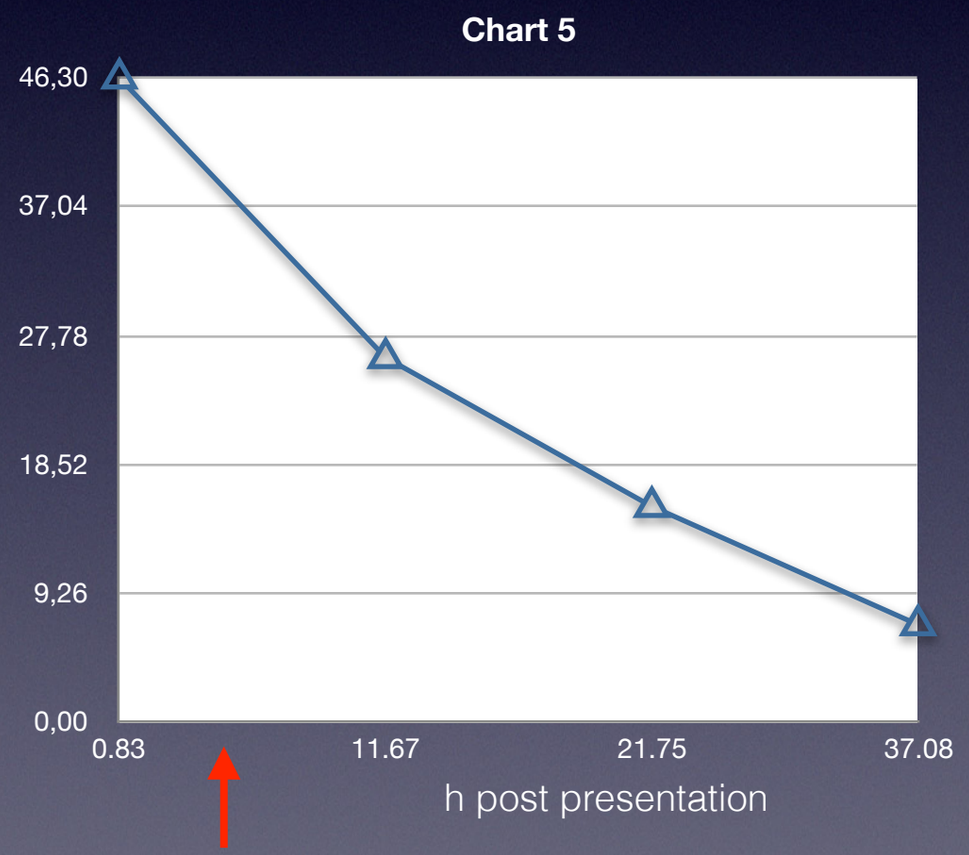
- carbamazepine concentration
  - therapeutic 4- 12 *μ*g/mL
  - **worry** > 35 *μ*g/mL
  - assays vary in how well that also measure 10,11 epoxide metabolite
- electrolytes (sodium)
- hepatic function

Management

- MDAC enhances elimination CBZ (enteroenteric clearance) and CBZ 10,11-epoxide (interrupts enterohepatic recirculation)
- Hemodialysis, consider for
  - seizures
  - arrhythmias
- Sodium bicarbonate boluses can be tried for QRS conduction disturbances

Back to case

- Endotracheal intubation
- Benzodiazepines for dystonia
- MDAC
- Extubation at 16 h post presentation



MDAC q 4 h
started 5 h post presentation

Oxcarbazepine

- CBZ analog, a prodrug
  - monohydroxycarbamazepine (MHD) is active drug
- less toxic than CBZ
- sedating
- MDAC enhances clearance of MHD
- may be some small cross reactivity OXC with CBZ assay
- like carbamazepine, hyponatremia an occasional complication

Lamotrigine

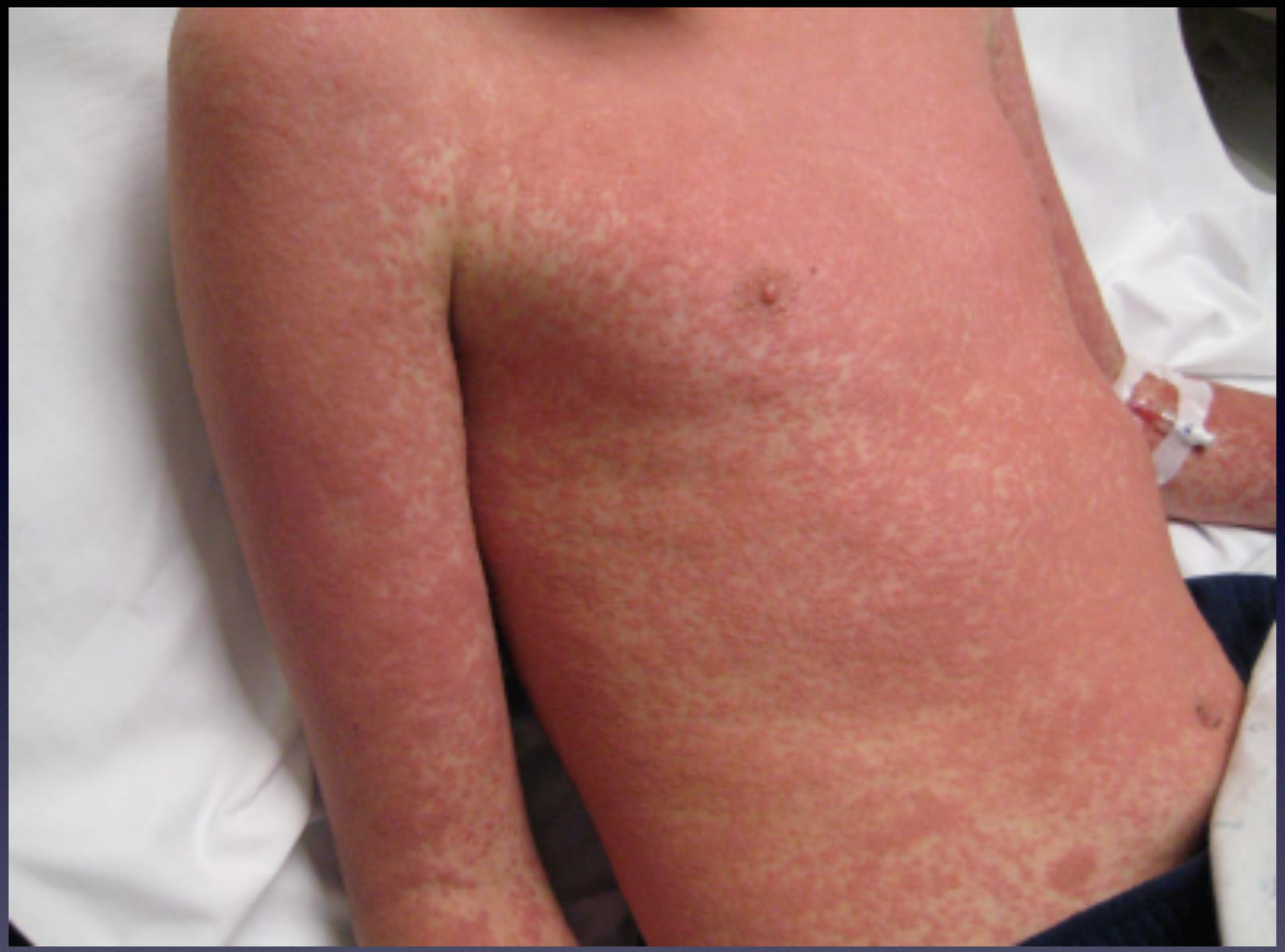
- sodium channel antagonism
- lethargy, ataxia, nystagmus
- look for QRS prolongation with overdose, seizures precautions
- management supportive, benzodiazepines, consider Na bicarbonate if ⬆ QRS
- lipid emulsion has been successfully used

Levetiracetam

- sedating
- be more worried of any co-ingestants

DRESS Syndrome

- Drug Reaction with Eosinophilia and Systemic Symptoms
  - anticonvulsant hypersensitivity syndrome PLUS systemic illness
  - fever, rash, solid organ involvement (esp. liver)
  - aromatic anti-seizure meds: phenytoin, CBZ, oxcarbazepine, phenobarbital, primidone, lamotrigine
  - non-aromatic levetiracetam has also been reported in literature



Clin Toxicol 2008;46:1093-4

	Seizure	Conduction Disturbance	MDAC	Hemodialysis
carbamazepaine	x	x	x	x
oxcarbazepine			x	
topiramate	x			
phenytoin	?		x	x
lamotrigine	x	x		
valproic acid	x		x	x
gabapentin	?			
pregabalin	*			
phenobarbital			x	x

* seizures reported with abuse

American Journal of Therapeutics 21, 265–268 (2014)

The Toxic Trio: Valproic Acid, Lithium, and Carbamazepine

Harry Karydes, DO,[1] Timothy J. Meehan, MD, MPH,[2]
and Sean M. Bryant, MD[3,4,5*]

Patients with altered mental status and seizure or psychiatric disease often present with an unclear medication history. Commonly prescribed medications include valproic acid (VPA), lithium (Li), or carbamazepine (CZN) of which the regional poison center (RPC) often recommends obtaining these serum concentrations. Regularly ruling out supratherapeutic concentrations without a known history of ingestion may help direct care. Cases from the RPC coded as VPA, Li, and CZN, from January 1,

- valproic acid, lithium and carbamazepine
- all are commonly used for mood disorders
- any altered patient with history mood disturbance and etiology of altered state is unclear
    - consider empiric measurement of concentrations if etiology altered state unclear

Seizure medications

- recognize potential for seizures with large overdose with some of these medications: carbamazepine, lamotrigine, VPA, topiramate
- cardiac conduction disturbance: lamotrigine
- for most: supportive care
- hemodialysis: severe VPA, carbamazepine
- VPA, think carnitine