ASM III

Elaine Wirrell, M.D.

Disclosures

- Off-label uses of medications (all marked by *)
- Only generic names will be used
- Limited time – please see handout for further information

Objectives

Pharmacology, side effects and indications for:

- Vigabatrin
- Rufinamide
- Zonisamide
- Felbamate
- Clobazam
- ACTH
- Fenfluramine
- Stiripentol
- CBD
- Ketogenic Diet

FDA Pregnancy Classes

- **A-D and X**
- **C**
  - Either animal studies have shown adverse effects and there are no controlled studies in women OR
  - Studies in women and animals are not available
  - Drugs should be given only if the potential benefit justifies the potential risk to the fetus

Vigabatrin: Pharmacology

- 500 mg sachets and 500 mg tabs
- MOA:
  - *Irreversible* inhibitor of GABA transaminase
  - Inhibits mTOR pathway in animal models
- Dosing:
  - Infants: 50-150 mg/kg/d div bid
  - Adults: 1000-3000 mg/d div bid

Vigabatrin: Pharmacology

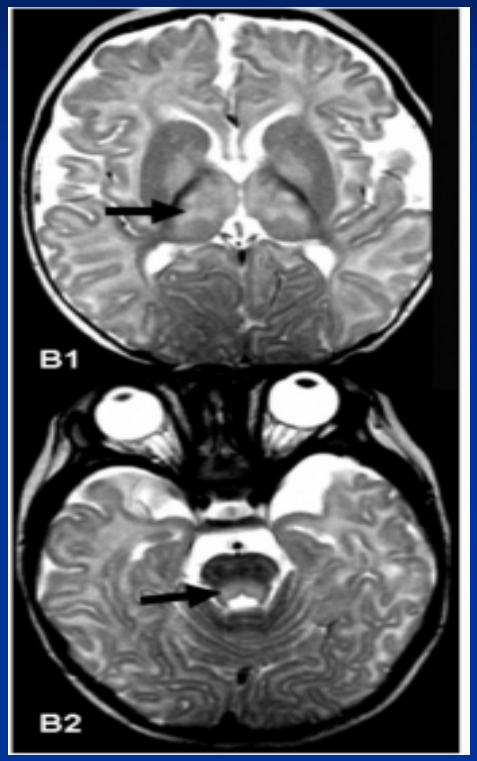
- No protein binding
- Most excreted renally unchanged
- T½ 10 hrs in adults, 6 hrs in infants – BID dosing

Vigabatrin: Side Effects

- Fatigue, somnolence or insomnia, dizziness
- Mood/behavior changes

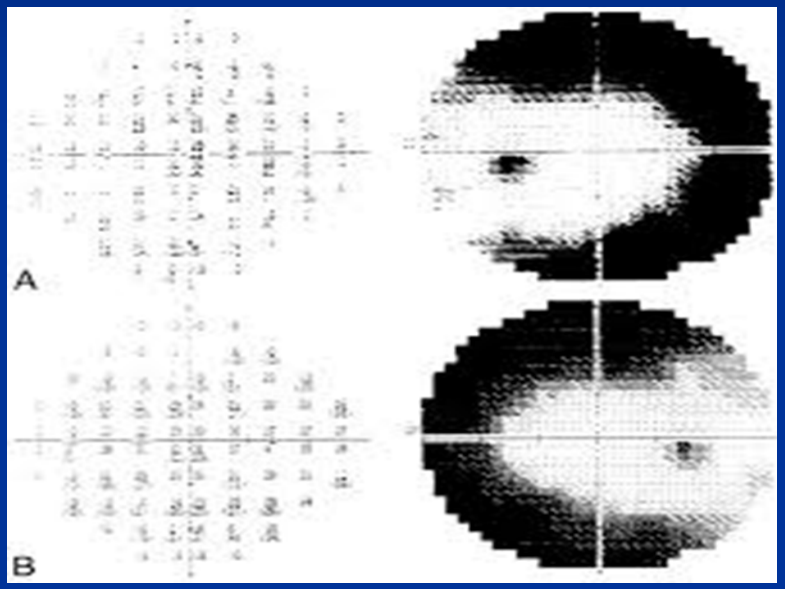
- Women:
  - No interaction with OCP
  - Pregnancy Class C

Vigabatrin: Intramyelinic Edema



- 20-30% develop T2 signal changes in basal ganglia, thalami, dentate, brainstem and cerebellum
- Most common in infants - often asymptomatic and resolves with time but not always!

Vigabatrin: Visual Field Deficits



- Slowly progressive, bilateral, concentric peripheral field loss, in 30-50%
- Not reversible
- Detection:
  - Perimetry
  - ERG – 30 Hz flicker
  - OCT to detect RNFL thinning

Vigabatrin: Indications

- West syndrome (esp. if due to TSC or FCD)
  - UKISS study: 54% spasm cessation at 2 wks
  - In TSC: 95% spasm cessation
  - Earlier treatment improves epilepsy and cognitive outcomes
- Intractable Focal Epilepsy (FDA >10 yrs of age)
  - Responder rates ≈50%, 5-10% sz-free

Lux et al. 2004, Hancock E et al. 1999, Jozwiak et al. 2011, French et al. 1996, Dean et al. 1999

Vigabatrin Access

- Through REMS program
- Providers must understand risks and need for periodic visual monitoring
- Must report potential serious side effects to REMS

Rufinamide: Pharmacology

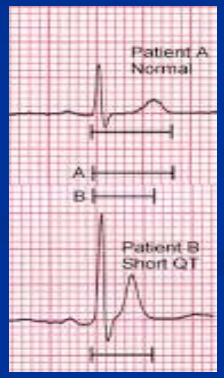
- 200 and 400 mg tabs, 40 mg/ml solution
- MOA:
  - Prolongs inactive state of Na channel
- Dosing:
  - Children 10-45 mg/kg/d div bid (5-30 if used with VPA)
  - Adults: 800-3200 mg/d div bid
  - Therapeutic levels: 5-30 mcg/mL

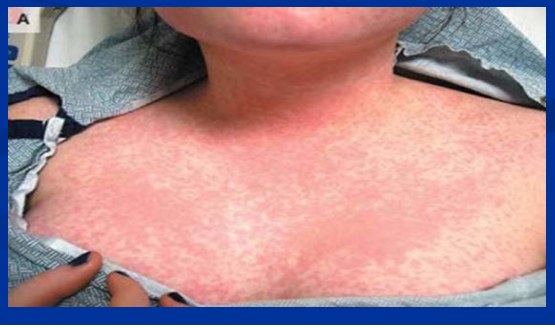
Rufinamide: Pharmcology

- Extensive hepatic metabolism, no active metabolites
- Renally excreted, low protein binding
- T½ ~ 6-10 hrs

Rufinamide: Side Effects

- QT shortening –EKG prior to initiation
- Rash - rarely SJS, DRESS
- Nausea, decreased appetite, weight loss
- Sleepiness, dizziness
- Women:
  - Pregnancy Class C
  - May affect efficacy of OCP





Rufinamide: Indications

- Adjunctive treatment for Lennox-Gastaut Syndrome >1 yr of age
  - Significant reduction in drop szs (-43% vs +1.5%), all seizures and seizure severity

- Refractory Focal Epilepsy*
  - Double-blind, placebo-controlled trial in ≥16 yrs showed significant reduction (-20.4% vs +1.6%)

Glauser et al. 2008, Brodie et al 2009, Kluger et al. 2009

Zonisamide: Pharmacology

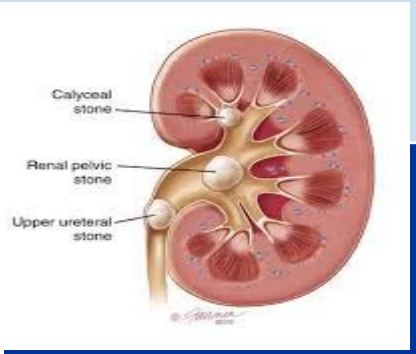
- 25, 50 and 100 mg
- MOA:
  - Blocks T type Ca channels, inhibits slow Na channels
  - Carbonic anhydrase inhibitor
- Dosing:
  - Children: 1-12 mg/kg/d div bid
  - Adults: 100-600 mg/d div bid
  - Therapeutic range: 10-40 mcg/mL

Zonisamide Pharmacology

- Long T½: 63 hrs
- Metabolized thru CYP 3A4, excreted predominantly in urine
- 40-60% protein bound

Zonisamide: Adverse Effects

Common	Rare
• Anorexia and weight loss • Fatigue • Cognitive slowing • Decreased sweating	• Nephrolithiasis • Glaucoma • Allergy - sulfa moiety, contraindicated in sulfa allergy -SJS, toxic epidermolysis (TEN) • Metabolic acidosis • Pancreatitis



Women:

- Pregnancy Class C
- No impact on OCPs

Zonisamide: Indications

- Adjunctive treatment of focal epilepsy ≥16 yrs
  - Responder rate 29-42% vs 10-22% for placebo
- Focal epilepsy in children*
  - 41-77% responders, up to 15% seizure-free

Brodie et al. 2005, Lee et al. 2010, Iinuma et al. 2004

Zonisamide: Indications

- Generalized epilepsy*
  - JME*: 80% responders
  - Refractory JAE*: 100% responders and 39% seizure-free
  - Absence seizures*: 51% seizure-free
- Infantile spasms (NOT FIRST LINE)*:
  - Symptomatic spasms: 26-36% resolution

Kothare et al. 2004, Velizarova et al. 2014, Wilfong et al. 2005, Yanai et al. 1999, Suzuki et al 1997, Lotze et al. 2004

Felbamate: Pharmacology

- 400 and 600 mg tabs, 120 mg/ml solution
- MOA:
  - Decreases excitation (blocks Na+ and Ca++ conductance)
  - Positive modulator of $GABA_A$

Felbamate: Dosing

- Children:
  - 15-45 mg/kg/d div tid
- Adults:
  - 400 mg-1200 mg tid
- Hepatic disease – contraindicated
- Adjust other co-therapies

Felbamate: Pharmacology

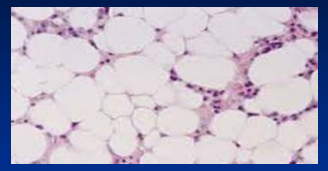
- Inhibits CYP450 – must adjust doses of many other AEDs
- 30-50% excreted in urine unchanged
- Low protein binding, T½ = 13-20 hrs

Felbamate: Adverse Effects

- Insomnia or sedation
- Anorexia, weight loss
- Occasionally psychosis, mood changes

- Women:
  - Pregnancy class C
  - May reduce efficacy of OCPs

Felbamate: Serious



- Hepatic toxicity:
  - 1/10,000 (lower in kids) usually within weeks of treatment
  - 2/3 progress to transplant or death within 4-6 weeks of symptom onset
- Aplastic Anemia:
  - 100 fold usual incidence (up to 1/5000)
  - Increased risk if cytopenia with other ASM or immune disorder

Felbamate: Indications

- Adjunctive therapy for Lennox-Gastaut (>2 years):
  - Drop seizures decrease by 34% and all seizures by 19-50%
- Intractable focal epilepsy (>14 years):
  - 52% responder rate

Felbamate study group 1993, Dodson 1993, Avanzini 1996, Sachdeo 1992, Faught 1993, Bourgeois 1991)

Felbamate: Indications

- Intractable focal epilepsy in children* - open-label studies:
  - Responder rates 52%, 10% sz-free
  - Reduction in sz frequency by 53%
- Generalized (non-LGS)* or undetermined epilepsy*:
  - Open label: 60% responder rate, 12% seizure-free

Carmant 1994, Avanzini 1996

Clobazam: Pharmacology

- 10 and 20 mg tab, 2.5 mg/ml suspension
- MOA: 1,5 benzodiazepine, $GABA_A$ agonist
- Active metabolite: nor-clobazam
- Children: 0.2-1.5 mg/kg/d div bid
- Adults: 5-40 mg/d
- Both CBD and STP increase levels of CLB and norCLB

Clobazam Pharmacology

- Excreted renally, mostly as metabolites
- T½ 18 hrs for CLB and 50 hrs for desmethylCLB

Clobazam: Side Effects

- Women:
  - Pregnancy Class C
  - No significant interaction with OCP
- Sedation
- Ataxia, dysarthria
- Aggression, irritability
- Rash – SJS/TEN rare <1/5000

Clobazam: Indications

- Adjunctive treatment in Lennox-Gastaut Syndrome (>2 years)
  - Reduction in drop szs by 68%
- Intractable epilepsy of all types*
  - 52-57% responders
  - 19% seizure-free

Ng et al. 2011, Koeppen et al. 1987, Montenegro et al. 2001, Kalra et al. 2010

Clobazam: Indications

- Monotherapy for children with focal epilepsy*
  - Children with new onset focal or GTC seizures
    - 56% remained on clobazam monotherapy at 1 yr
    - No significant difference from CBZ or PHT

Canadian Study Group for Childhood Epilepsy 1998 and 1999

ACTH

- Natural ACTH 80 IU/ml solution
- Synthetic ACTH – injection powder for solution 0.25 mg (=25 IU of ACTH)
- Given IM
- Dosing : both high (150 U/m2 div bid x 14 d, then taper off over next 2 weeks) and low dose (10-40 U/d) protocols have been used - no convincing evidence that high-dose is superior

ACTH: Pharmacology

- MOA:
  - Unknown but may reduce CRH, which is known to induce seizures
  - ?anti-inflammatory

ACTH: Side Effects

- Weight gain, puffiness
- Increased BP
- Increased glucose
- GI bleeding and abdominal upset
- Irritability
- Infection
- Fractures
- Addisonian crisis if tapered to rapidly

ACTH: Indications

- Infantile spasms
  - First line therapy, with exception of TSC
  - 60-70% efficacy at stopping spasms and resolving hypsarrhythmia
  - No evidence that high dose (4-8 mg/kg/d) oral steroid is inferior to ACTH (*Chang et al. 2019, Grinspan et al., in press*)
- Other intractable, early-onset, epileptic encephalopathies*
  - Benefit in isolated case reports

Riikonen 2014, Schmidt et al. 2000

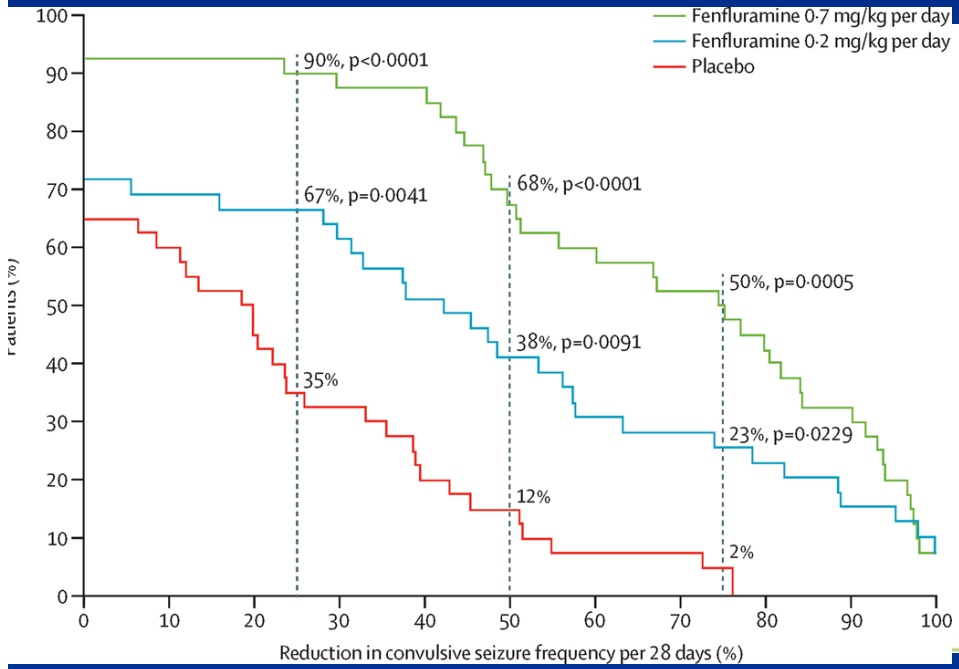
Fenfluramine: Pharmacology

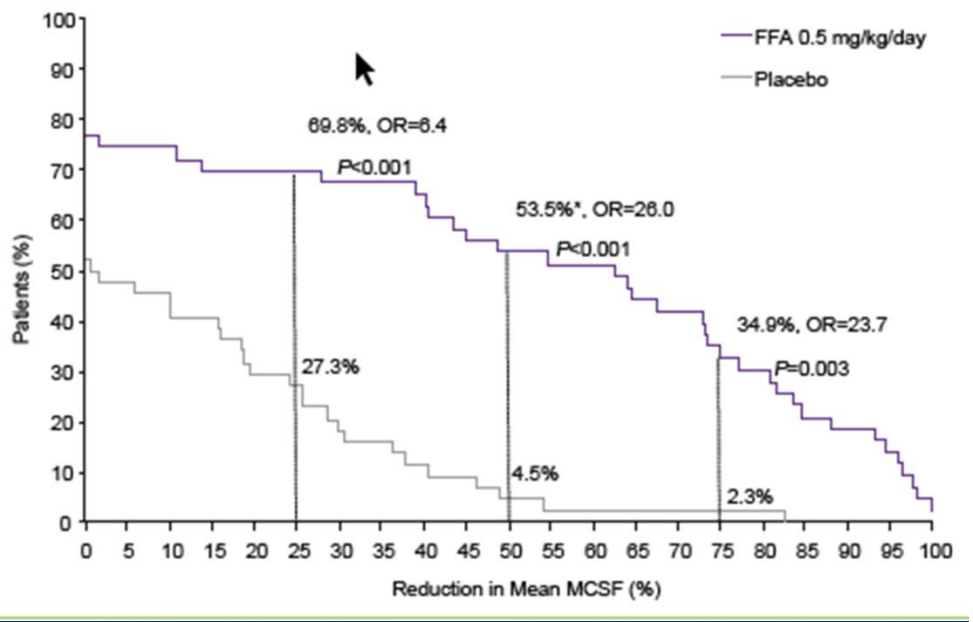
- Oral solution 2.2 mg/ml
- Exact MOA unclear:
  - Serotonergic action
  - Positive modulator of sigma receptors
- Dosing
  - Without stiripentol – 0.2-0.7 mg/kg/d (max 27 mg)
  - With stiripentol – 0.2-0.4 mg/kg/d (max 17 mg)

Fenfluramine side effects

- Decreased appetite, diarrhea, vomiting, weight loss
- Sedation, lethargy
- Potential for serotonin syndrome – caution if using with SSRIs or serotonergic agents
- When used at higher doses, with phentermine for obesity – valvular heart disease, pulmonary hypertension – not seen in clinical trials in Dravet

Fenfluramine Indication: Dravet syndrome >2 years of age





No STP

With STP

Fenfluramine Access

- Through REMS program
- Providers must understand possible cardiac risk and counselling and report any cardiac findings
- Patients need baseline Echo, then q6 months
- Echo also needed 3 months after discontinuation

Stiripentol: Pharmacology

- 250 and 500 mg tabs and sachets
- Multiple MOA:
  - $GABA_A$ergic
  - Neuroprotective
- Dosing: 20-50 mg/kg/d div bid (teens/adults - lower mg/kg doses)
- Increases levels of both clobazam and carbamazepine

Stiripentol Pharmacology

- Highly protein bound
- Extensive hepatic metabolism to inactive metabolites
- Inhibits CYP2C19 and 3A4, with significant increases in clobazam and carbamazepine levels

Stiripentol: Side Effects

- Nausea, anorexia, weight loss
- Sedation, ataxia
- Rare, transient neutropenia
- Women:
  - Pregnancy Class C
  - No significant interaction with OCPs

Stiripentol: Indications

- Dravet syndrome: (>2 years)
  - Add-on CLB – 70% responders
  - Reduces SE and ER visits
- Intractable focal epilepsy*:
  - 57% responder rate
- 2 case series suggesting efficacy in refractory status epilepticus*

Chiron et al. 2000, Perez et al. 1999, Chiron et al 2006, Strzelczyk et al. 2015, Uchida et al. 2017

Cannabidiol

- Will refer ONLY to the pharma-grade FDA approved product
- Artisinal products often have variable amounts of THC and CBD and are not considered equivalent to pharma-grade CBD

Cannabidiol (pharma-grade): Pharmacology

- 100 mg/ml solution in oil
- MOA unknown – not due to effect on CB1 and CB2 receptors
- Inhibits metabolism of CLB and nor-CLB
- Dosing:
  - Target dose 10-20 mg/kg/d – can achieve target dose within 2 weeks

Cannabidiol: Pharmacology

- Highly protein-bound
- Hepatic metabolism
- T½ 18-32 hours

Cannabidiol: Side Effects

- Adverse effects (usually self-limited):
  - Somnolence, fatigue
  - Diarrhea, anorexia, weight loss
  - Increased liver enzymes (with VPA)
- Women:
  - Pregnancy class C
  - May reduce efficacy of OCPs

Cannabidiol: Indications

- Dravet syndrome (>2 yrs):
  - median reduction in convulsive szs of 39% vs 13% (p=0.01)
- Lennox-Gastaut (>2 yrs):
  - median reduction in drop/convulsive szs of 44% vs 22% (p=0.01)
- TSC (>2 yrs):
  - 36-40% responders (at 25 and 50 mg/kg, respectively) vs 22% on placebo

Devinsky et al. 2017 and 2018, Thiele et al. 2019 (abstract)

Ketogenic Diet

- High fat, low CHO diet
- MOA:
  - Multiple possible, unclear which one(s) result in improved seizures
- Side Effects:
  - Early: Food refusal, vomiting, hypoglycemia, ketoacidosis and exacerbation of underlying metabolic disorder
  - Later: Hyperlipidemia, pancreatitis, constipation, cardiomyopathy, kidney stones

Ketogenic Diet

- Subtypes:
  - ***Classical diet*** – ketogenic ratio (g fat/g CHO + pro) typically ranges from 2:1 to 4:1
  - ***Modified Atkins*** – lower ratio. Count carbs (10-20g/d) and encourage fat
  - ***Low Glycemic Index*** – lowest ratio. Limit carbs to 40-60 g/d and only use CHO with glycemic index<50

Ketogenic Diet

- Absolute contraindications:
  - Disorder of FA oxidation
  - Pyruvate carboxylase deficiency
  - Carnitine deficiency
  - Porphyria
- Relative contraindications:
  - Significant hyperlipidemia
  - Kidney stones

Ketogenic Diet

- Indications:
  - Absolute: GLUT1 deficiency, pyruvate dehydrogenase deficiency
  - Often considered early for early onset, epileptic encephalopathies without clear surgical focus
- A knowledgeable dietician is essential for implementation

Ketogenic Diet

- Efficacy in children:
  - 50% have a >50% reduction in seizures
  - 33% have a >90% reduction in seizures
  - 15% seizure free
- Efficacy in adults:
  - 35% responders
  - SRSE: 79% responders

Kossoff and Rho 2009, Cervanka et al. 2016, Cervanka et al. 2017

Conclusions

- When choosing an ASM:
  - Efficacy for syndrome/etiology/seizure type?
  - Is it safe?
  - Is it reasonable for this patient? – sex, co-morbidities, other medical problems, other medications, ease of use
- If meds fail, is dietary therapy a reasonable option?