

Pharmacology 101: Anti-Epileptic Drugs

DSF Biennial Family
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Michelle Welborn, PharmD



Objectives

- Receive Practical Advice Regarding Prescription Medications
- Understand the Absorption, Distribution, Metabolism and Excretion of Drugs
- Understand Mechanisms AED Interactions and Adverse Reactions
- Gain better understanding of how to avoid interactions and adverse reactions and how to discuss pharmacology of AEDs with healthcare providers



Practical Advice

- Follow through with monitoring blood levels when appropriate (*ADME*)
- Weekly pill boxes may reduce medication administration errors
- Know what tablets can be crushed or split (*absorption*)
- Pay attention to recommended storage conditions AND DO not pre-fill any liquid medications into smaller containers, vials or syringes unless stability information is available from a physician, pharmacist, or manufacturer (*stability*)
- If the medication is in an amber colored bottle or is contained in a foil wrapper, there is a reason (*stability*)
- The taste of medications can often be masked

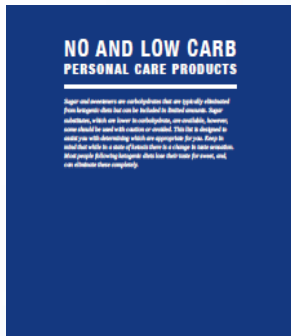


Practical Advice



- Using syringe adapters on bottles may decrease the risk of contamination

- Watch carb content when on ketogenic diet (good time to switch from liquids to tablets or capsules)



- Have an emergency seizure treatment protocol that includes what drugs to avoid signed by the neurologist

- Discuss creating a “sick protocol” with the neurologist

- Rectal acetaminophen suppositories are great for fever when patients have GI illness

- Strive to be open minded to returning to drug that previously didn't give the anticipated response, as long as it is not contraindicated



Seizure Activity: A Delicate Balance

Excitation (lots of firing)
Na⁺ and Ca⁺⁺ inside cell

GLUTAMATE RELEASE



Inhibition (balancing the firing)

Cl⁻ – inside cell; K⁺ outside cell

GABA RELEASE

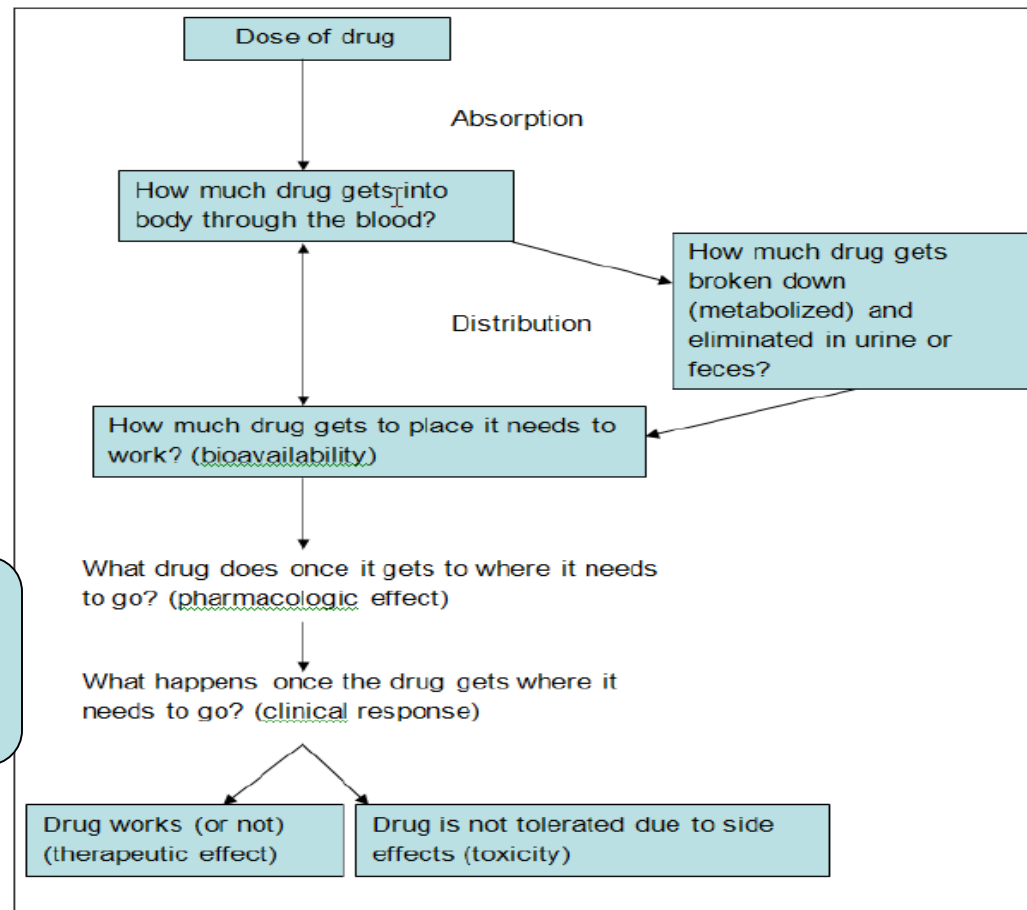


Stomach to Brain – Pharmacokinetics and Pharmacodynamics of Anti-epileptic drugs (AEDs)

Figure 1: General principles of pharmacokinetics

Pharmacokinetics =
What body does to drug

Pharmacodynamics =
What drug does to body



Pharmacokinetics of AEDs

- Absorption
- Distribution
- Metabolism
- Elimination

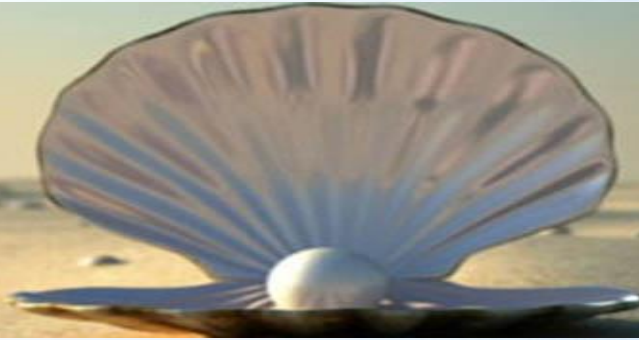


Useful Terms

- T_{max} : time to maximum drug concentration
- C_{max}: maximum drug concentration
- AUC: amount of drug under the time/concentration curve
- Half life (t_{1/2}) : Time it takes for ½ of drug to be eliminated from body
- Steady state: Absorption = Elimination



Clinical Pearl:
How long does
drug stay in
system?



- Common question – how long will it take for the drug to get out of his system?
- It typically takes about 5 half lives to clear a drug from the body after discontinuation of the drug
- “Steady state” pharmacokinetics occur in the same amount of time

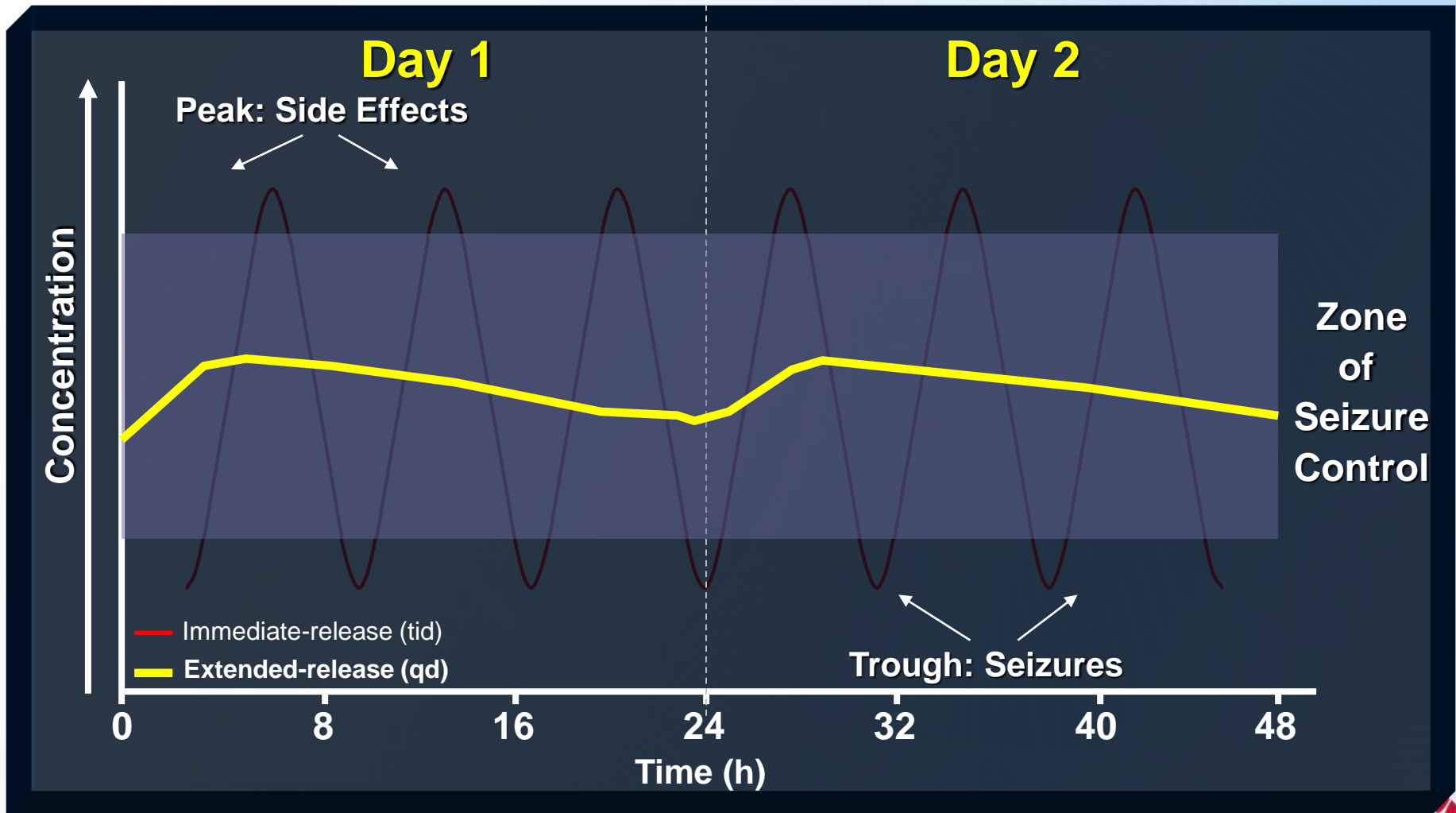
Example:

Phenobarbital $t_{1/2} = 2 - 7$ DAYS

Lamotrigine $t_{1/2} = 13.5$ HOURS



Pharmacokinetics



Clinical Pearl:
What if she
throws up?



First step: Look at emesis

Think about: Liquid versus tablet or capsule, outside coating, how often drug is taken



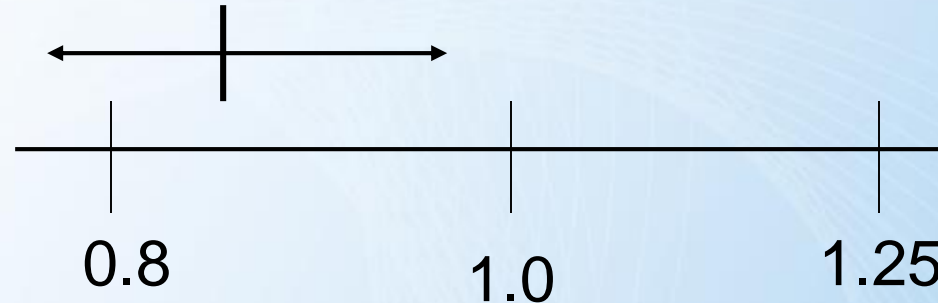
Bioequivalence of Drugs: FDA Accepted Parameters

- Single dose of reference drug and test drug given to healthy adults in a crossover design. Bioequivalence accepted when the 90% confidence interval of the ratios
 - AUC
 - C_{\max}
 - T_{\max}
- The bioequivalence interval falls between 0.8 and 1.25 (log-transformed data)

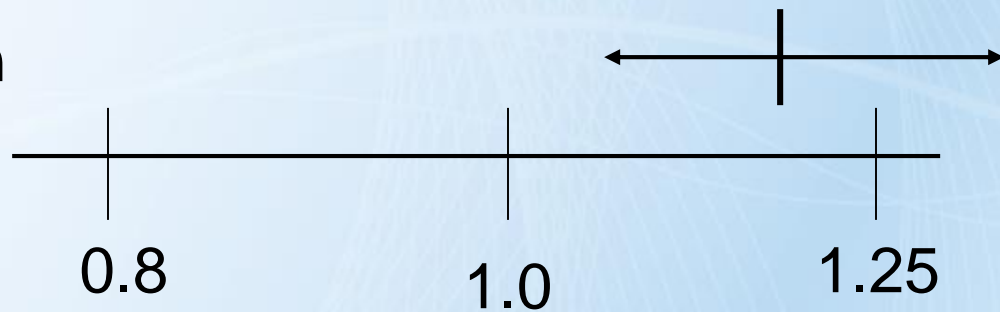


Testing for Bioequivalence

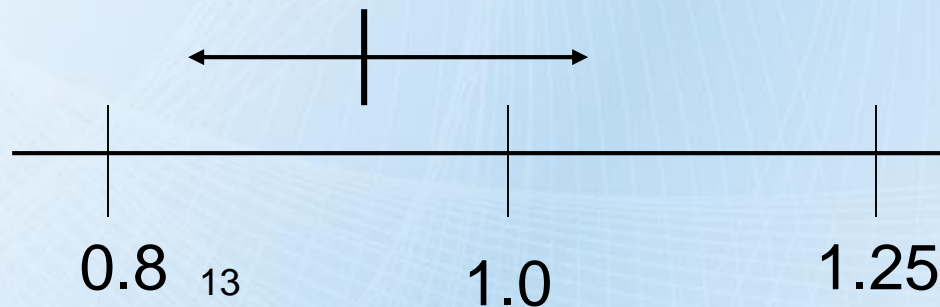
Test product low nonequivalent



Test product high nonequivalent

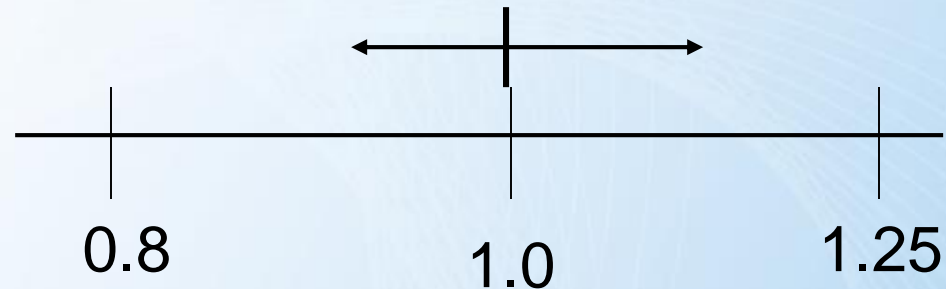


Test product bioequivalent

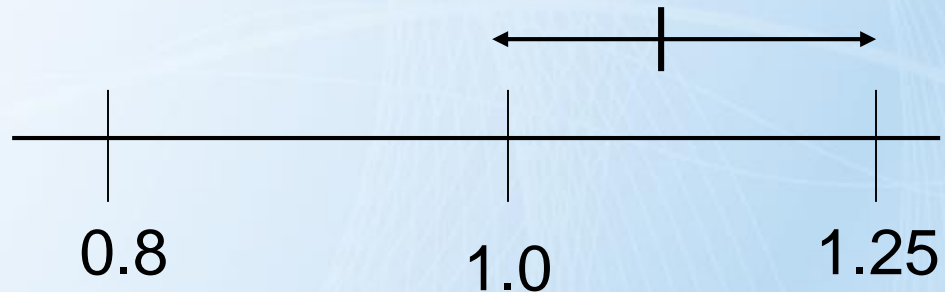


Bioequivalence : Generic/Generic

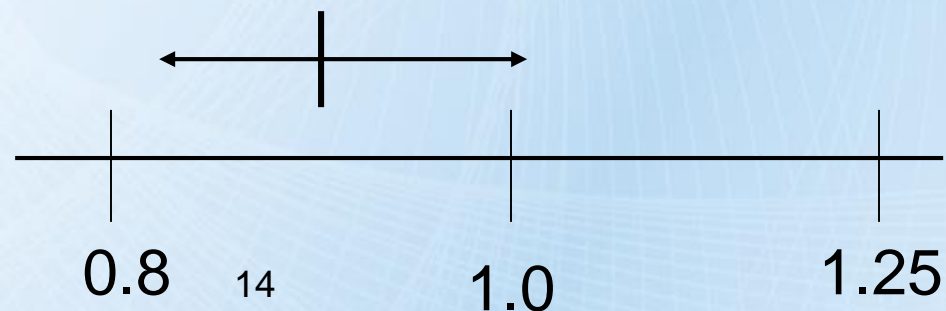
Brand Product



Generic #1



Generic #2



Clinical Pearls



Generic AEDs

- Speak to the pharmacist about the importance of using the same generic manufacturer for each refill

Drug Stability

- Stability tests are conducted during drug development based on various conditions. It is important to follow manufacturers recommendation on storage conditions and expiration.

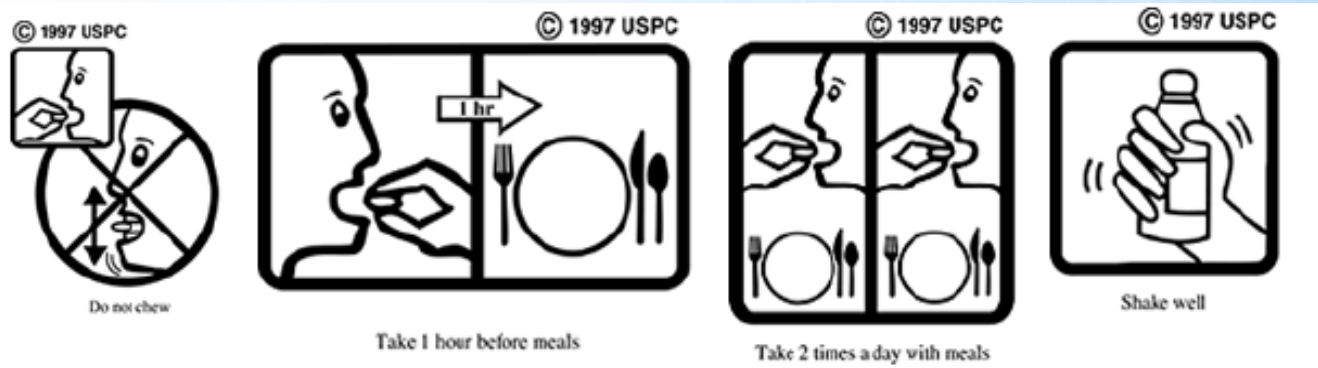


Mechanisms of Drug Interactions

- Absorption Inhibition
- Metabolic Enzyme Inhibition
- Metabolic Enzyme Induction
- Additive Pharmacodynamic Effects
- Antagonistic Pharmacodynamic Effects



Absorption Inhibition



- Binding to cations such as aluminum, magnesium, iron, calcium (multi-vitamins, supplements)
- pH dependent absorption – pH in stomach changed by drug or food (dairy, acidic fruits or vegetables)
- Full or empty stomach ?



Pharmacogenomics

- Genetic variability (also known as polymorphism) influences metabolism
- POLG DNA testing prior to use of valproic acid
- 1/5 people of Asian decent are poor metabolizers of drugs dependent on CYP2C19 enzyme for metabolism (phenytoin, phenobarbital)
- The future of pharmacotherapy.....

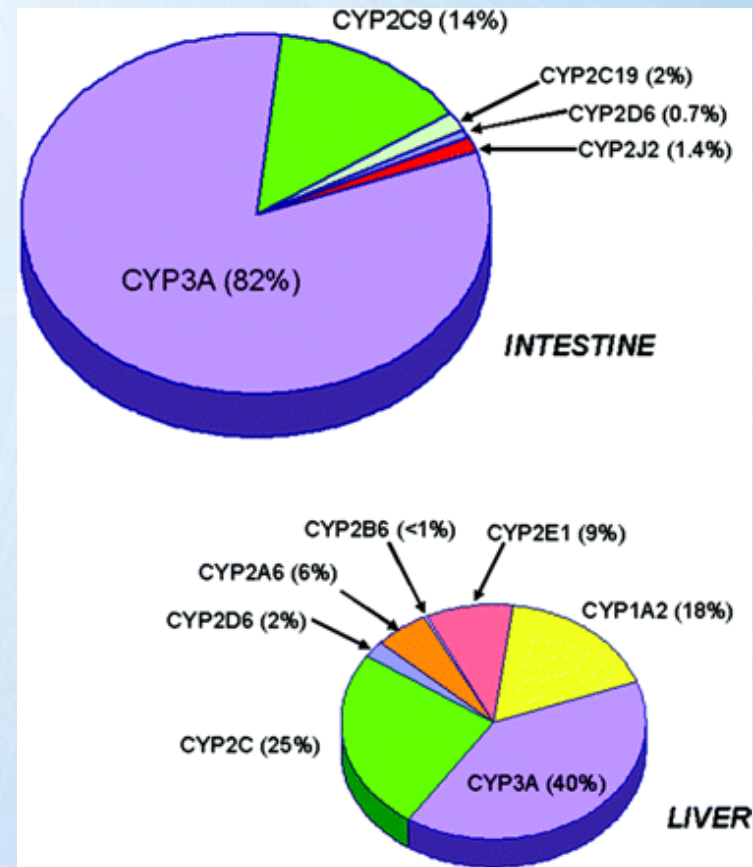


Enzyme Inhibition

- Resource to check for drug interactions

www.drugs.com/drug_interactions.html

- Use with caution and consult prescriber or pharmacist



Enzyme Induction

- Enzyme inducers increase the activity of certain metabolizing enzymes, thereby decrease effect of drugs dependent on these enzymes for metabolism
 - Carbamazepine, phenytoin, primidone (Mysoline), phenobarbital



Pharmacodynamic Interactions

- Antagonistic Interactions (increases risk of seizures)
 - Giving drugs that can decrease seizure threshold to person with epilepsy
 - Propofol (anesthetic)
 - Certain high dose antibiotics
 - Aminophylline (bronchodilator)
 - Cyclosporin
 - Oral contraceptives
 - Stimulants
 - Anti-psychotics



Pharmacodynamic Synergy



- Polytherapy required for Dravet Syndrome
- Classic synergistic drug cocktail for Dravet Syndrome: stiripentol, clobazam, valproic acid
- All medication changes (including OTC or herbal therapy) should be under the supervision of the treating neurologist
- Consideration of continued need of AED should be made as new drugs are added



Food and Herbs that Alter Drug Metabolism

- St John's Wort
- Milk Thistle
- Garlic
- Ginseng
- Licorice
- Grapefruit



Herbal Pharmacodynamic Interactions

- Herbs that can decrease seizure threshold
 - Ginkgo biloba
 - Star fruit
 - Star nise
 - Sage
 - Ephedra
 - Eucalyptus
 - Pennyroyal
 - Shankhapusphi



Conclusion

- Understanding fundamental pharmacology may help facilitate discussion with healthcare providers and make informed decisions
- Herbs are not necessarily benign and may interact with AEDs – any use of herbal therapy should be discussed with neurologist before use



Questions?

