Antiepileptic Drug (AED) Pharmacokinetics and Therapeutic Drug Monitoring in Children

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Memphis, TN    USA
Pharmacodynamic Effect

Pharmacokinetic Characteristics

DRUG

PATIENT
AED Pharmacokinetics: Definitions

- **Pharmacokinetics**: study of the movement or passage of drugs through the body.
  - How frequently? (clearance, t½)
  - Time to steady state? (TSS=5-7x t½)

- **Pharmacodynamics**: evaluation of the effect or physiological response a medication has through its actions on a receptor.
  - Safe and effective dose

- **Developmental Pharmacokinetics**: how maturation affects disposition of AEDs.

- **Pharmacogenetics**: study of inter-individual variation in DNA sequences related to drug response
Developmental Changes in Physiologic Factors That Influence Drug Disposition

Developmental Changes in Hepatic Function

Absorption

- Antacids impair absorption: ↓PB, PHT, CBZ, GBP levels
- Food may slow rate of absorption (↑Tmax)
  - PB, VPA-DR, LTG, TPM, LEV, ZNS, PRP
    (no change in AUC)
- peak serum levels (TGB)
- bioavailability (Tegretol-XR, OXC-XR, RFM)
- Dose-dependent: GBP, RFM
- Developmental changes: ↓PHT, CBZ in first two years of life
Antiepileptic Drugs that are Converted to Active Metabolites

<table>
<thead>
<tr>
<th>AED</th>
<th>Active Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primidone</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td></td>
</tr>
<tr>
<td>Acetate (ESL)</td>
<td></td>
</tr>
</tbody>
</table>
Antiepileptic Drugs that are Converted to Active Metabolites

<table>
<thead>
<tr>
<th>AED</th>
<th>Active Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primidone</td>
<td>Phenobarbital &amp; Phenylethylmalonic Acid (PEMA)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Carbamazepine epoxide</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>MHD (10-monohydroxy derivatives (R- &amp; S-) of OXC)</td>
</tr>
<tr>
<td>Eslicarbazepine Acetate</td>
<td>Eslicarbazepine (S-MHD of OXC)</td>
</tr>
</tbody>
</table>
Distribution

• **Protein binding**
  – High (>65%): PHT, CBZ, VPA, TGB, DZP, EZG, CLB, PER
  – Low (<60%): PB, FLB, GBP*, LTG, TPM, ZNS, ESL LEV*, OXC, VGB*, PGB, LCS*, RFM
  – Important in low albumin states, co-administration of other highly protein-bound drugs, infants.

• **Lipid solubility**
  – Loading dose (mg) = Vd x (∆p conc.) x wt. (kg)
Determining a Loading Dose of an AED

Dose (mg) = \text{Weight (kg)} \times V_D (L/kg) \times \text{Change in concentration}

V_D = \text{Volume of distribution}

\text{Change in concentration} = \text{Desired AED level} - \text{Current AED level}
**Volumes of Distribution ($V_D$) for Parenteral AEDs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean $V_D$ (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>0.75</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.6</td>
</tr>
<tr>
<td>Valproate Sodium</td>
<td>0.22</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0.50</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>0.50 (?)</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>0.04</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.8-2.0</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Calculation of a Parenteral Loading Dose

Fosphenytoin

• Phenytoin level = 6 µg/mL
• Weight = 60 kg
• Desired phenytoin level = 16 µg/mL
• Fos-PHT dose (mg) = 60 x 0.75 x (16-6)
  = 450 mg fosphenytoin
AED Levels and Disease State

The effects of liver and renal disease on the pharmacokinetics of the AEDs is dependent on the pathways of elimination of the AEDs.

The effects of liver and renal disease on the pharmacokinetics of the AEDs is dependent on the pathways of elimination of the AEDs.
Excretion (Elimination)

• Renally excreted drugs accumulate if creatinine clearance decreases.

» Gabapentin, Vigabatrin
» Levetiracetam, Pregabalin
» Topiramate, Zonisamide, Oxcarbazepine, Lacsoamide, Ezogabine, Eslicarbazepine
AED Elimination

• **Renal Elimination**
  - Gabapentin, Pregabalin, Levetiracetam, Vigabatrin

• **Mixed Renal and Hepatic**
  - Phenobarbital, Felbamate, Oxcarbazepine, Eslicarbazepine, Topiramate, Zonisamide, Lacosamide, Ezogabine

• **Hepatic**
  - Cytochrome P450: Carbamazepine, Phenytoin, Tiagabine, Clobazam, Perampanel
  - UGT: Lamotrigine
  - Non-CYP or UGT: Oxcarbazepine, Eslicarbazepine, Rufinamide, Levetiracetam, Ezogabine
Hepatic Metabolism

• Most clinically significant interactions arise via interference with liver metabolism.

• AED’s that are not metabolized and completely excreted:
  
  PGB, GBP and VGB

• AED that undergoes non-hepatic metabolism:
  
  LEV
Metabolic Drug Interactions

- Hepatic Enzyme Induction
  
  [Drug A] + Inducer

- Hepatic Enzyme Inhibition

  [Drug B] + Inhibitor → [Drug B]

Time Course

0 1d 7d 14d
Hepatic Induction

- PB, PRM, PHT, CBZ
  CYP* & UGT* systems induced
- OCZ, ESL, TPM, RFM
  weak inducers CYP3A4
- LTG, VPA
  weak inducer UGT

*CYP=cytochrome P450,
*UGT=uridine diphosphateglucuronosyltransferase
Mechanism of Induction of CYP3A4-Mediated Metabolism

Wilkinson GR, NEJM; 2005, 352: 2211-21
AEDs and Oral Contraceptives (OCP)

AEDs That Reduce The Efficacy Of OCPs

- Phenobarbital
- Phenytoin
- Carbamazepine
- Primidone
- Oxcarbazepine
- Eslicarbazepine
- Felbamate
- Rufinamide
- Topiramate (dose-dependent, >200mg/d)
- Clobazam
- Perampanel
AEDs and Oral Contraceptives (OCP)

AEDs That Do Not Reduce The Efficacy of OCPs

- Gabapentin
- Lamotrigine
- Zonisamide
- Topiramate (<200mg/d)
- Ezogabine
- Levetiracetam
- Tiagabine
- Valproate
- Pregabalin
- Vigabatrin
- Lacosamide
16 year old female (55 kg)
- Complex partial seizure disorder for 3 years.
- On combination-type OCP for 2 years.
- Current medication
  - Lamotrigine 100 mg, 3 BID
  - OCP
- No seizures for 1 year, regular menses
AED Drug Interactions
Case Study (cont.)

- OCP discontinued
- About 8 days later
  - Complains of nausea, some emesis
  - Ataxic

What happened?
How do you improve her symptoms?
## UGT Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on UGT</th>
<th>Resulting LTG Serum Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Induction</td>
<td>↘</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Induction</td>
<td>↘</td>
</tr>
<tr>
<td>OCP (ethinylestradiol)</td>
<td>Induction</td>
<td>↘</td>
</tr>
<tr>
<td>Valproate</td>
<td>Inhibition</td>
<td>↑</td>
</tr>
</tbody>
</table>

Christensen J et al, Epilepsia, 2007; 48(3): 484-489
AED Drug Interactions
De-Induction

- Serum lamotrigine level obtained: 12.8
  - Serum lamotrigine level when on OCPs was 7

- Decision
  - Lamotrigine decreased to 200 mg bid

- Follow-up
  - Side-effects resolved
  - Seizure free
  - Lamotrigine level 8.3
Hepatic Inhibition

- VPA inhibits: CYP2C9 isozymes
  UGT
  Epoxide hydrolase
  Carboxylesterases

- FLB inhibits: CYP2C19
  Beta oxidation

- TPM, OCZ, ESL inhibit CYP2C19
VPA Inhibition of LTG: Relationship to VPA Concentration

EC_{50} = 4.6 \mu g/ml
EC_{90} = 38.7 \mu g/ml

Goals of Extended-Release Formulations

- **Peak-Related Toxicity**
- **Subtherapeutic Trough - Risk of Seizures**
- **Therapeutic Range**
- **MTC**
- **MEC**

Twice-Daily Dosing vs. Once-Daily Dosing

## Extended Release Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Brand Name</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin Sodium Capsules</td>
<td>qd</td>
<td>Dilantin</td>
<td>30, 100 mg</td>
</tr>
<tr>
<td>Carbamazepine ER Tablets ER Capsule</td>
<td>BID</td>
<td>Tegretol XR</td>
<td>100, 200, 400 mg</td>
</tr>
<tr>
<td></td>
<td>BID</td>
<td>Carbatrol</td>
<td>100, 200, 300 mg</td>
</tr>
<tr>
<td>Divalproex Sodium ER Tablet</td>
<td>qd</td>
<td>Depakote ER</td>
<td>250, 500 mg</td>
</tr>
<tr>
<td>Gabapentin Enacarbil ER Tablet</td>
<td>qd</td>
<td>Horizant ER</td>
<td>300, 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gralise</td>
<td>300, 600 mg</td>
</tr>
<tr>
<td>Lamotrigine ER Tablet</td>
<td>qd</td>
<td>Lamictal XR</td>
<td>25, 50, 100, 200, 250, 300 mg</td>
</tr>
<tr>
<td>Topiramate ER Capsule</td>
<td>qd</td>
<td>Trokendi XR</td>
<td>25, 50, 100, 200 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Qudexy XR</td>
<td>25, 50, 100, 150, 200 mg</td>
</tr>
<tr>
<td>Levetiracetam ER Tablet</td>
<td>qd</td>
<td>Keppra XR</td>
<td>500, 750 mg</td>
</tr>
<tr>
<td>Oxcarbazepine ER Tablet</td>
<td>qd</td>
<td>Oxtellar XR</td>
<td>150, 300, 600 mg</td>
</tr>
</tbody>
</table>
No Need for Extended Release Formulation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>t½ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital (Luminal)</td>
<td>60 – 180</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)</td>
<td>30 – 40</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
<td>63</td>
</tr>
<tr>
<td>Clobazam (Onfi)</td>
<td>36 – 42</td>
</tr>
<tr>
<td>(N-desmethyl clobazam)</td>
<td>(71 – 82)</td>
</tr>
<tr>
<td>Perampanel (Fycompa)</td>
<td>105</td>
</tr>
<tr>
<td>Eslicarbazepine (Aptiom)</td>
<td>20 - 24</td>
</tr>
</tbody>
</table>

What Does That Leave?
## Not Available In ER Formulation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>$t^{1/2}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamatate (Felbatol)</td>
<td>20 - 23</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>2 – 9</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>6.3</td>
</tr>
<tr>
<td>Rufinamide (Banzel)</td>
<td>6 – 10</td>
</tr>
<tr>
<td>Lacosamide (Vimpat)</td>
<td>13</td>
</tr>
</tbody>
</table>
Why Extended Release Products?

1. Better Seizure Control
   - Better adherence
   - Independent of adherence

2. Minimize Drug Toxicity

How Do I Dose Them?

1. Twice Daily!

Pharmacogenetics & The Treatment of Epilepsy

Pharmacogenetics Began in 1956
Pharmacogenetics Began in 1956

Association of hemolytic anemia in patients treated with primaquine (for malaria) and G6PD deficiency.
BIOTRANSFORMATION

3 CYP families (1,2,3)

7 primary isozymes

CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4

Antiepileptic Drug Interactions

Genetic Polymorphism

- 15 year-old male, cryptogenic complex partial seizures, new onset
- Phenytoin 300 mg/day (4 mg/kg/day)
- Two weeks later – seizure free
- Symptoms: fatigue, nystagmus, slight ataxia
- Phenytoin level 38 – *WHY?*
Genetic Polymorphism

- **CYP2C9** – poor metabolizers, 2-6% Caucasian
- **CYP2D6**
  - inactive form in 5-10% Caucasian
  - 1-3% Asian
- **CYP2C19**
  - absent 2-6% Caucasian
  - 20% Asian

Genelex, AmpliChip Cytochrome P-450 genotype test, Affymetrix GeneChip Microarray Instrumentation System, Baylor College of Medicine Medical Genetics Laboratory are FDA approved to detect genetic variants of CYP2D6 and CYP2C19 isozymes. CYP2C9 Genelex, Mayo Lab or ARUP.

Phillips KA et al, JAMA, 2001; 286 (18): 2270-2279
## Polymorphisms in AED-Metabolizing Genes

### Defective Alleles (%)

<table>
<thead>
<tr>
<th>P-450</th>
<th>Drug</th>
<th>Caucasian</th>
<th>Asian</th>
<th>African</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C9</td>
<td>Phenytoin</td>
<td>8-10</td>
<td>1-2</td>
<td>1</td>
<td>↓ Clearance↑ Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>Phenytoin Felbamate</td>
<td>15</td>
<td>35</td>
<td>17</td>
<td>↓ Clearance↑ Toxicity</td>
</tr>
<tr>
<td></td>
<td>Diazepam Diazepam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A6</td>
<td>Valproate</td>
<td>2-4</td>
<td>15-20</td>
<td>0</td>
<td>↓ Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4*1B</td>
<td>Carbamazepine</td>
<td>4-11</td>
<td>0</td>
<td>53-69</td>
<td>↓ Clearance↑ Toxicity</td>
</tr>
<tr>
<td></td>
<td>Ethosuximide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiagabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

www.cypalleles.ki.se

Current and Future Approaches to Pharmacologic Management of Disease

(Pharmacogenetics)
## Pharmacogenetics: Carbamazepine, HLA Allele + Risk of SJS

<table>
<thead>
<tr>
<th>Author</th>
<th>HLA Allele</th>
<th>Population</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung WH</td>
<td>HLA-B* 1502</td>
<td>Han Chinese</td>
<td>2,504</td>
</tr>
<tr>
<td>Limdi N</td>
<td>HLA-B* 1502</td>
<td>Hong Kong, Malaysia, Thailand, Philippines, Taiwan (Indians, Japan, Korea less)</td>
<td></td>
</tr>
<tr>
<td>Ozeki T</td>
<td>HLA-A* 3101</td>
<td>Japan</td>
<td>34</td>
</tr>
<tr>
<td>McCormack M</td>
<td>HLA-A* 3101</td>
<td>European</td>
<td>26</td>
</tr>
</tbody>
</table>

# Drug Specific HLA Associations

<table>
<thead>
<tr>
<th>Medicine</th>
<th>DRESS (Drug Rash with Eosinophilia and Systematic Symptoms)</th>
<th>Risk</th>
<th>Associated HLA</th>
<th>SJS / TEN (Stevens Johnson Syndrome / Toxic Epidermal Necrolysis)</th>
<th>Risk</th>
<th>Associated HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>High</td>
<td>High</td>
<td>HLA-A*3101</td>
<td>High</td>
<td>HLA-B*3101 (White)</td>
<td>HLA-B*1502 (Asian)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HLA-B*1502 (Asian)</td>
<td></td>
<td>HLA-B*5901 (Japanese)</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>High</td>
<td>High</td>
<td></td>
<td>High</td>
<td>HLA-B*1502 (Asian)</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>High</td>
<td>High</td>
<td></td>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>High</td>
<td>High</td>
<td>HLA-B*3801</td>
<td></td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

(High = ≥ 1 per 10,000 users; Incidence)

Stern RS. NEJM, 2012; 366: 2492-2501
Clinical Pharmacogenetics Implementation Consortium Guidelines

• How to interpret HLA-B* 15:02 genotype tests to guide the use of carbamazepine\(^1\)
• Therapeutic recommendations for codeine based on \(CYP2D6\) genotype\(^2\)
• Recommendations for the use of phenytoin based on \(CYP2C9\) and/or HLA-B genotype\(^3\)
• All available on: PharmGKB; [www.pharmgkb.org](http://www.pharmgkb.org)

Special Report

Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies

*Philip N. Patsalos, †David J. Berry, ‡Blaise F. D. Bourgeois, §James C. Cloyd, ¶Tracy A. Glauser, #Svein I. Johannessen, $Illo E. Leppik, **Torbjörn Tomson, and ††Emilio Perucca

*Institute of Neurology/The National Hospital for Neurology and Neurosurgery, London and The Chalfont Centre for Epilepsy, Chalfont St Peter, United Kingdom; †Medical Toxicology Unit, Guys and St. Thomas’ Hospital, London, United Kingdom; ‡Harvard Medical School, Children’s Hospital Boston, Boston, Massachusetts, U.S.A.; §Center for Orphan Drug Research, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, U.S.A.; ¶Children’s Hospital Medical Center, Department of Neurology, Cincinnati, Ohio, U.S.A.; #The National Center for Epilepsy, Sandvika, Division of Clinical Neuroscience, Rikshospitalet University Hospital, Oslo, Norway; $University of Minnesota, Minneapolis, Minnesota, U.S.A.; **Karolinska University Hospital, Stockholm, Sweden; and ††Institute of Neurology, IRCCS C. Mondino Foundation and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy
Therapeutic Drug Monitoring: Situations in Which AED Measurements Are Likely to Be of Benefit

• Establish baseline individual therapeutic concentration.
• Evaluate potential causes for lack of efficacy:
  – Fast metabolizers
  – Partial adherence (Noncompliance)
• Evaluate potential causes for toxicity:
  – Altered drug utilization as a consequence of physiological conditions (puberty, geriatrics)
  – Slow metabolizers
  – Altered drug utilization as a consequence of pathological conditions (renal failure, liver failure)
  – Drug-drug interactions

Therapeutic Drug Monitoring: Situations in Which AED Measurements Are Likely to Be of Benefit

- Guide dose adjustments in situations with increased pharmacokinetic variability, or anticipated change:
  - Altered drug utilization as a consequence of physiological conditions (e.g. neonates, infants, young children, and pregnancy)
  - Altered drug utilization as a consequence of pathological conditions.
  - Change in formulation.
  - Drug drug interaction.
- Judge “room to move” or when to change AEDs.
- Minimize predictable problems (PHT, VPA).
<table>
<thead>
<tr>
<th>AED</th>
<th>Reference Range (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>3 - 12</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40 – 100</td>
</tr>
<tr>
<td>Ezogabine</td>
<td>.5 – 1.5</td>
</tr>
<tr>
<td>Felbamate</td>
<td>30 - 100</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4 - 20</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>3 - 12</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2 - 20</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20 - 60</td>
</tr>
<tr>
<td>Oxcarbazepine, Eslicarbazepine (MHD)</td>
<td>10 – 45</td>
</tr>
<tr>
<td>Perampametal</td>
<td>.3 - 1.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>2 - 16</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>15 - 40</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>5 - 70</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2 - 20</td>
</tr>
<tr>
<td>Valproate</td>
<td>50 - 100</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>10 - 40</td>
</tr>
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REMEMBER:

PHARMACOKINETICS, PHARMACOGENETICS AND PHARMACODYNAMICS IS PHUN!
EFFECT OF PHENOBARBITAL ON OTHER ANTIEPILEPTIC DRUGS

Induces CYP2C and CYP3A families and UGT

Induction begins within 1 week. Maximal induction 2-3 weeks. Deinduction 2-3 weeks after removal.

↓, ↑, ↔ PHT (CYP2C9, CYP2C19 induction)
↓ CBZ (induces 3A4 & ↑ 10, 11 epoxide (40%)
↓ LTG (UGT), ↓ TPM (CYP), TGB (3A4), VPA (2C9 & 2C19, UGT), OXC (UGT), ZNS (3A4, 2C19)
EFFECT OF OTHER AED’S ON PHENOBARBITAL

75% HEPATIC:
20% METABOLIZED BY CYP2C9, 30% N-GLYCOSIDE
25% RENAL ELIMINATION

PHT ↑ PB : 20% CYP2C9

VPA ↑ PB
EFFECT OF PHENYTOIN ON OTHER ANTIEPILEPTIC DRUGS

- **INDUCES CYP2C19 AND CYP3A FAMILIES AND UGT**
- **INHIBITS CYP2C9**

- **INDUCTION BEGINS WITHIN 1 WEEK.**
- **MAXIMAL INDUCTION 2-3 WEEKS.**
- **DEINDUCTION 2-3 WEEKS AFTER REMOVAL.**

↓ CBZ (CYP3A4)

↓ LTG (UGT), TGB (CYP3A4), TPM (CYP3A4)

↓ VPA (all pathways)

↓ OXC (UGT), ZNS (CYP3A, 2C19)
100% HEPATIC: 90% METABOLIZED BY CYP2C9(80%), CYP2C19(20%)

CBZ and PB, ↓ PHT (induces 2C19)
VGB- ↓ PHT approx. 30%

FBM (inhibits 2C19) ↑ PHT
VPA (inhibits 2C9) ↑ PHT
TPM, OCZ (inhibit 2C19) - ↑ PHT
EFFECT OF CARBAMAZEPINE ON OTHER ANTIEPILEPTIC DRUGS

INDUCES CYP2C9, CYP2C19 AND CYP3A4 FAMILIES AS WELL AS SOME UGTs

↓ FBM (CYP3A4), TGB (CYP3A4)
↓ TPM (CYP), VPA (CYP2C)
↓ LTG (UGT)
↓ CBZ (Autoinduction)
↓ OXC (UGT), ZNS (CYP3A4, 2C19)
EFFECT OF OTHER AED’S ON CARBAMAZEPINE

100% HEPATIC:
65% METABOLIZED BY CYP3A4, CYP2C8, CYP1A2; 15% UGT

PB, PHT, FBM ↓ CBZ (induces CYP3A4)

VPA (inhibits epoxide hydrolase) ↑ 10,11-epoxide CBZ
EFFECT OF VALPROATE ON OTHER ANTIEPILEPTIC DRUGS

INHIBITS CYP2C9, UGT, EPOXIDE HYDROLASE AND BETA-OXIDATION

↑ PB (inhibits 2C9 & UGT)
  PHT (inhibits 2C9)
  CBZ 10, 11 epoxide (inhibits epoxide hydrolase)
  FBM, LTG, LRZ (inhibits UGT)

↓ CBZ (induces CYP3A4)
EFFECT OF OTHER AED’S ON VALPROATE

100% HEPATIC:
10% METABOLIZED BY CYP2C9, CYP2C19, CYP2A6;
30% BETA-OXIDATION

60% GLUCURONIDATION (UGT2B1)

PB (2C9) , PHT (2C19) , CBZ (2C9) , LTG (UGT)
↓ VPA

FBM (inhibits beta oxidation) ↑ VPA
EFFECT OF FELBAMATE ON OTHER ANTIEPILEPTIC DRUGS

INDUCES CYP3A4; INHIBITS CYP2C19, EPOXIDE HYDROLASE and BETA-OXIDATION

↑ PB, PHT (INHIBITS 2C19)
↑ VPA (INHIBITS BETA OXIDATION)
↑ CBZ 10, 11 epoxide (INDUCES 3A4; INHIBITS EPOXIDE HYDROLASE)

↓ CBZ (INDUCES 3A4)
FBM

hydroxylation

epoxidation

10,11 epoxide

epoxide hydroxylase

10,11 trandiol

glucuronidation

FBM

glucuronidation

O-S-C-NH2-Glcuronide
EFFECT OF OTHER AED'S ON FELBAMATE

15% METABOLIZED BY CYP3A4, CYP2E1; 10% UGT; 25% HYDROLYSIS; 50% UNCHANGED

PB (3A4), PHT (3A4 & UGT), CBZ (3A4) ↓ FBM

VPA (INHIBITS UGT) ↑ FBM
GABAPENTIN DRUG INTERACTIONS

DOES NOT AFFECT THE CYP SYSTEM

100% RENAL EXCRETION

DOES NOT AFFECT OTHER AEDs.
NO CHANGE IN SERUM LEVELS BY OTHER AEDs
EFFECT OF LAMOTRIGINE ON OTHER ANTIEPILEPTIC DRUGS

WEAK INDUCER OF UGT

↓ VPA (~25%) and LTG (autoinduction of UGT)
EFFECT OF OTHER AED’S ON LAMOTRIGINE

90% HEPATIC:  
0% METABOLIZED BY CYP FAMILIES; 65% UGT1A4  
7% RENAL

PB, PRM, PHT, CBZ, OXC (INDUCES UGT) ↓ LTG  
OCP, ACETAMINOPHEN ↓ LTG (BY 50,15%)  

VPA ↑ LTG (INHIBITS UGT)
EFFECT OF TOPIRAMATE ON OTHER ANTIEPILEPTIC DRUGS

INDUCER OF BETA-OXIDATION; INHIBITOR OF CYP2C19

↑ PHT - INHIBITS 2C19 (AT HIGHER PHT LEVELS)

↓ VPA - INDUCES BETA OXIDATION (↓ ~ 12%)
EFFECT OF OTHER AED’S ON TOPIRAMATE

HEPATIC 40% TO 70%
15% METABOLIZED (CYP ? ISOENZYMES)
60% RENAL

PB, PHT, CBZ (INDUCE CYP) ↓ TPM
VPA (BETA OXIDATION INDUCTION) ↓ TPM (14%)
EFFECT OF TIAGABINE ON OTHER ANTIEPILEPTIC DRUGS

DOES NOT AFFECT THE CYP SYSTEM

↓ VPA (11%)
EFFECT OF OTHER AED’S ON TIAGABINE

100% HEPATIC:
> 30% METABOLIZED CYP3A4

PB, PHT, CBZ (3A4) ↓ TGB (40 - 50%)
LEVETIRACETAM DRUG INTERACTIONS

66% RENAL EXCRETION
34% NON-HEPATIC METABOLISM (HYDROLYSIS)

DOES NOT AFFECT OTHER AEDs
NO CHANGE IN LEV SERUM LEVELS BY OTHER AEDs
EFFECT OF OXCARBAZEPENE ON OTHER ANTIEPILEPTIC DRUGS

- MILD INDUCER OF CYP3A4, UGT;
  MILD INHIBITOR OF CYP2C19

- PHT (UP TO 40%)
  - PB (15% - INHIBITS CYP2C19)

- VPA (~ 18% - INDUCES UGT)
- LTG (~ 29%)
EFFECT OF OTHER AEDs ON OXCARBAZEPINE

100% HEPATIC: UGT

PB, PHT, PRM, CBZ - ↓ OXC (29 - 40%)
EFFECT OF ZONISAMIDE ON OTHER ANTIEPILEPTIC DRUGS

NO EFFECT IN CLINICAL TRIALS
EFFECT OF OTHER AED'S ON ZONISAMIDE

HEPATIC 50 - 70%
(METABOLIZED CYP3A4, CYP2C19, CYP3A5)
RENAL 30 - 50%

PB, PHT, CBZ, (CYP) ↓ ZNS (40 - 50%)
PREGABALIN DRUG INTERACTIONS

DOES NOT AFFECT THE CYP SYSTEM

98% RENAL EXCRETION

DOES NOT AFFECT OTHER AEDs.
NO CHANGE IN SERUM LEVELS BY OTHER AEDs
EFFECT OF RUFINAMIDE ON OTHER ANTIEPILEPTIC DRUGS

NO EFFECT IN CLINICAL TRIALS
EFFECT OF OTHER AED’S ON RUFINAMIDE

HEPATIC 98%
(METABOLIZED: Carboxylesterase Hydrolysis, non-P450)

PB, PRM, PHT, CBZ ↓ RFM (20 - 45%)
VPA ↑ RFM Up To 70 %
EFFECT OF CLOBAZAM ON OTHER ANTIEPILEPTIC DRUGS

NO EFFECT IN CLINICAL TRIALS
EFFECT OF OTHER AED’S ON CLOBAZAM

HEPATIC 98%
(METABOLIZED: CYP3A4 > 2C19)

CLB Inhibits CYP2D6.
Alcohol Increases CLB by 50%.
Poor-metabolizers of CYP2C19 have increased N-desmethyl metabolites of CLB.
EFFECT OF EZOGABINE ON OTHER ANTIEPILEPTIC DRUGS

↓ LTG ~ 15%
EFFECT OF OTHER AED’S ON EZOGABINE

HEPATIC ~ 65%
(METABOLIZED UGT1A1)
RENAL 85%

PHT, CBZ (UGT) ↓ EZG (~ 30%)
EFFECT OF PERAMpanel ON OTHER ANTIEPILEPTIC DRUGS

↑ OXC ~ 25%
EFFECT OF OTHER AED’S ON PERAMPANEL

HEPATIC ~ 85%
(METABOLIZED CYP3A4 > 3A5)

PHT, CBZ, OXC (CYP3A4) ↓ PRP (~ 50-65%);
TPM ↓ PRP ~20%
EFFECT OF ESLICARBIZEPINE ON OTHER ANTIEPILEPTIC DRUGS

- MILD INDUCER OF CYP3A4, MILD INHIBITOR OF CYP2C19
- ↑ PHENYTOIN LEVELS
EFFECT OF OTHER AEDs ON ESLICARBAZEPINE

1/3 HEPATIC: UGT
2/3 RENAL

PB, PHT, PRM, CBZ - ↓ MHD-OXC LEVELS
SELECTED REFERENCES:


SELECTED REFERENCES (cont’d):


SELECTED REFERENCES (cont’d):


