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# AEDs and Drug Interactions

**Objectives:**

- Identify at least three drug-drug interactions in AEDs.
- Able to use at least 2 AEDs as adjunctive therapy with synergistic effect.
- Able to identify idiosyncratic reactions in AEDs.
- Able to identify the effects AEDs have on co-morbidities.

# Drug Interactions of AEDs

# AEDs and Drug Interactions

- To predict Drug Interactions of AEDs, one needs to understand the pharmacological properties of AEDs including their pharmacokinetics and pharmacodynamics.

# AEDs and Drug Interactions

**Definitions:**

- AEDs: Antiepileptic Drugs are used for the treatment of Epilepsy and Seizures.
- Pharmacokinetics: Study of the movement and effects of a drug across compartments in the body.
- Pharmacodynamics: Study of the response of a drug when it has been delivered to the site of mechanism of action.

# AEDs and Drug Interactions

**Definitions:**

- Pharmacokinetics: Examines absorption, distribution, metabolism and clearance of drugs.
  - Examples: Serum concentration of an AED; protein-binding.
- Pharmacodynamics: Examines receptor binding and effects on physiological or cellular properties from drugs.
  - Examples:  Efficacy decreasing seizure rate; Sedation

# TABLE 65-4 Antiepileptic Drug Pharmacokinetic Data

| AED | $t_{1/2}$ (h) | Time to steady state (days) |
|---|---|---|
| Carbamazepine | 12 M; 5–14 Co | 21–28 for completion of auto-induction |
| Ethosuximide | A 60; C 30 | 6–12 |
| Felbamate | 16–22 | 5–7 |
| Gabapentin[a] | 5–40[b] | 1–2 |
| Lacosamide | 13 | 3 |
| Lamotrigine | 25.4 M | 3–15 |
| Levetiracetam | 7–10 | 2 |
| Oxcarbazepine | 3–13 | 2 |
| Phenobarbital | A 46–136; C 37–73 | 14–21 |
| Phenytoin | A 10–34; C 5–14 | 7–28 |
| Pregabalin | A6-7[b] | 1–2 |
| Primidone | A 3.3–19; C 4.5–11 | 1–4 |
| Rufinamide | 6–10 | 2 |
| Tiagabine | 5–13 | |
| Topiramate | 18–21 | 4–5 |
| Valproic acid | A 8–20; C 7–14 | 1–3 |
| Vigabatrin | 5-8 | N/A |
| Zonisamide | 24–60 | 5–15 |

Rogers SJ, Cavazos JE. In DiPiro's Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

# TABLE 65-4 Antiepileptic Drug Pharmacokinetic Data

| AED | Clinically Important Metabolite | Protein Binding (%) |
|---|---|---|
| Carbamazepine | 10,11-epoxide | 40–90 |
| Ethosuximide | No | 0 |
| Felbamate | No | ~25 |
| Gabapentin[a] | No | 0 |
| Lacosamide | No | <15 |
| Lamotrigine | No | 40–50 |
| Levetiracetam | No | <10 |
| Oxcarbazepine | 10-hydroxy-carbazepine | 40 |
| Phenobarbital | No | 50 |
| Phenytoin | No | 90 |
| Pregabalin | No | 0 |
| Primidone | PB | 80 |
| Rufinamide | No | 26–35 |
| Tiagabine | No | 95 |
| Topiramate | No | 15 |
| Valproic acid | May contribute to toxicity | 90–95 binding saturates |
| Vigabatrin | No | 0 |
| Zonisamide | No | 40–60 |

Rogers SJ, Cavazos JE. In DiPiro's Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

# AEDs and Drug Interactions

- Main principles:
  - It takes 5 half-lives to get to 95% of steady state,
  - IV load is to get to steady state ASAP,
  - Serum concentrations can be measured at 1-2 hrs,
  - Concentrations that are “therapeutic” are trough levels,
  - Maintenance drug should be given at 2 hrs after load

Rogers SJ, Cavazos JE. In DiPiro’s Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

# AEDs and Drug Interactions

- Main principles:
  - If AED has a high protein binding, oral dosing with a meal or a protein supplement will delay absorption.
  - Some drugs have higher affinity to protein than others. If Valproate IV is given in a patient taking chronically Phenytoin, the Valproate IV will displace Phenytoin from binding sites, creating a transient Phenytoin toxicity with no change in total (but an increase “free”) Phenytoin level.

Rogers SJ, Cavazos JE. In DiPiro’s Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

**TABLE 65-7** Antiepileptic Drugs Elimination Pathways and Major Effects on Hepatic Enzymes

| Antiepileptic Drugs | Major Hepatic Enzymes |
|---|---|
| Carbamazepine | CYP3A4; CYP1A2; CYP2C8 |
| Ethosuximide | CYP3A4 |
| Felbamate | CYP3A4; CYP2E1; other |
| Gabapentin | None |
| Lacosamide | CYP2C19 |
| Lamotrigine | GT |
| Levetiracetam | None (undergoes non-hepatic hydrolysis) |
| Oxcarbazepine (MHD is active oxcarbazepine metabolite) | Cytosolic system |
| Phenobarbital | CYP2C9; other |
| Phenytoin | CYP2C9; CYP2C19 |
| Pregabalin | None |
| Rufinamide | Hydrolysis |
| Tiagabine | CYP3A4 |
| Topiramate | Not known |
| Valproate | GT; $\beta$-oxidation |
| Vigabatrin | None |
| Zonisamide | CYP3A4 |

Rogers SJ, Cavazos JE. In DiPiro's Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

**TABLE 65-7** Antiepileptic Drugs Elimination Pathways and Major Effects on Hepatic Enzymes

| Antiepileptic Drugs | Induced | Inhibited |
|---|---|---|
| Carbamazepine | CYP1A2; CYP2C; CYP3A; GT | None |
| Ethosuximide | None | None |
| Felbamate | CYP3A4 | CYP2C19; $\beta$-oxidation |
| Gabapentin | None | None |
| Lacosamide | None | None |
| Lamotrigine | GT | None |
| Levetiracetam | None | None |
| Oxcarbazepine (MHD is active oxcarbazepine metabolite) | CYP3A4; CYP3A5; GT | CYP2C19 |
| Phenobarbital | CYP3A; CYP2C; GT | None |
| Phenytoin | CYP3A; CYP2C; GT | |
| Pregabalin | None | None |
| Rufinamide | CYP3A4 (weak) | CYP2E1 (weak) |
| Tiagabine | None | None |
| Topiramate | CYP3A (dose dependent) | CYP2C19 |
| Valproate | None | CYP2C9; GT epoxide hydrolase |
| Vigabatrin | CYP2C9 | None |
| Zonisamide | None | None |

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# AEDs and Drug Interactions

- Main principle:
  - Example: Phenytoin is primarily metabolized by CYP 2C9 and 2C19, and Carbamazepine induces all CYP 2C hepatic isoenzymes. The effect of adding Carbamazepine to chronic Phenytoin will result in a reduction of Phenytoin level, due to an increase efficiency of 2C9 and 2C19 metabolism.

Rogers SJ, Cavazos JE. In DiPiro's Pharmacotherapy, 8th Edition, McGraw-Hill, 2011

# AEDs that induce CYP 3A4

- Carbamazepine
- Felbamate
- Oxcarbazepine
- Phenobarbital
- Phenytoin

- Rufinamide (weak)
- Topiramate (dose dependent)
- Lamotrigine (over 400 mg/d)

# Common Drugs metabolized by CYP 3A4

- Alpra-, tria-, mida-zolam
- Amitriptyline
- Calcium channel blockers
- Carbamazepine
- Corticosteroids
- Digoxin
- Cyclosporin
- Methadone
- Pimozide
- Protease inhibitors (HIV)
- Quinidine
- Statins (cholesterol)
- Terfenadine
- Vitamin D (osteoporosis)
- Some chemotherapy drugs

# Synergism and Antagonism of combinations of AEDs

- Synergism:  1 + 1 = 3

  You get more effect than the effect of just simply adding to drugs.

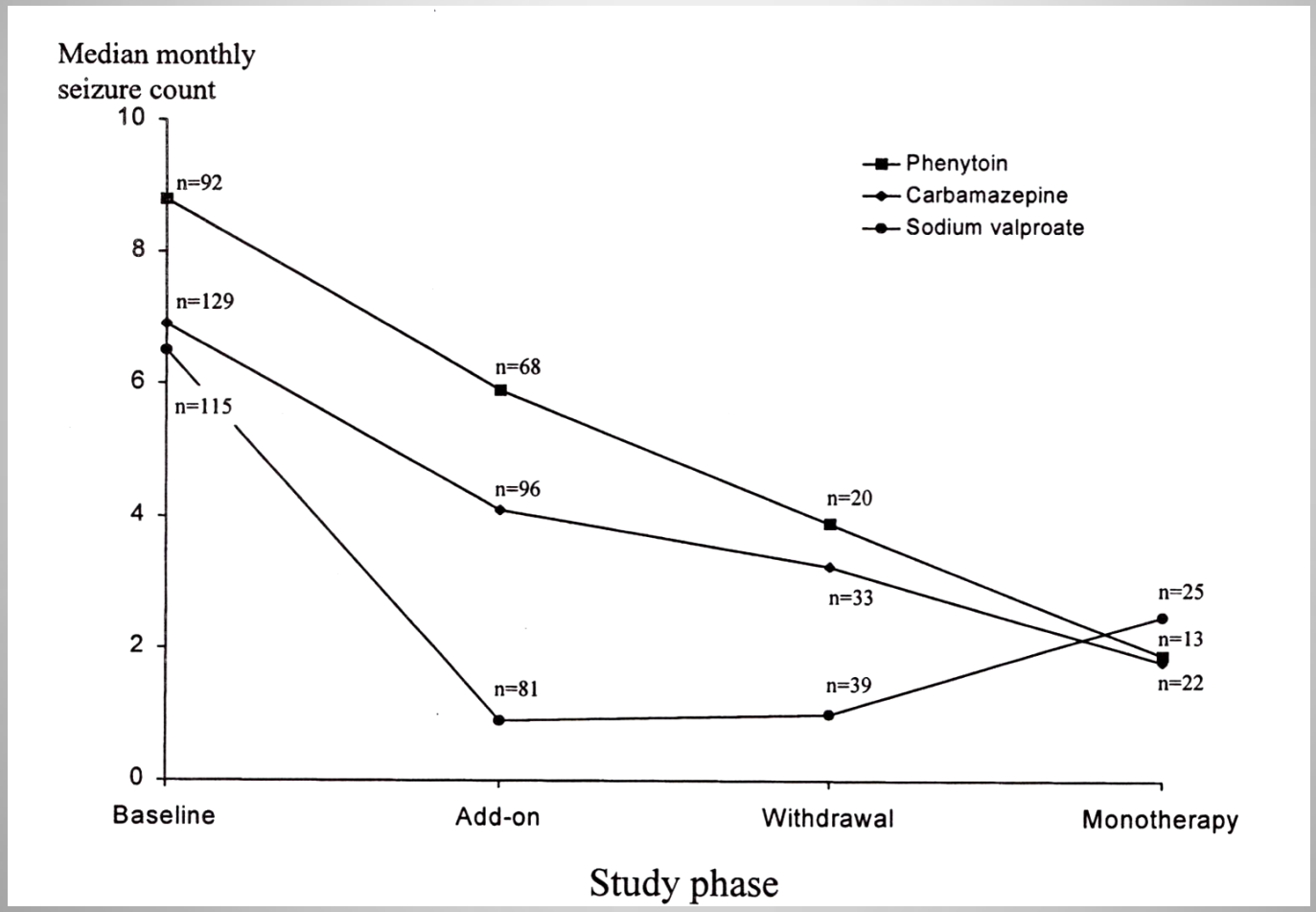
  Example: 2 sedative drugs are worse combined

- Antagonism: 3 – 1 = 1

  You get less effect than the effect of just simply subtracting drugs.

  Example: An alerting drug added to sedative drug

# LTG 105 Study: LTG added to CBZ or VPA then if success conversion to monotherapy




LTG plasma levels slightly higher add-on in VPA, but identical to CBZ during withdrawal.

Brodie et al., 1997

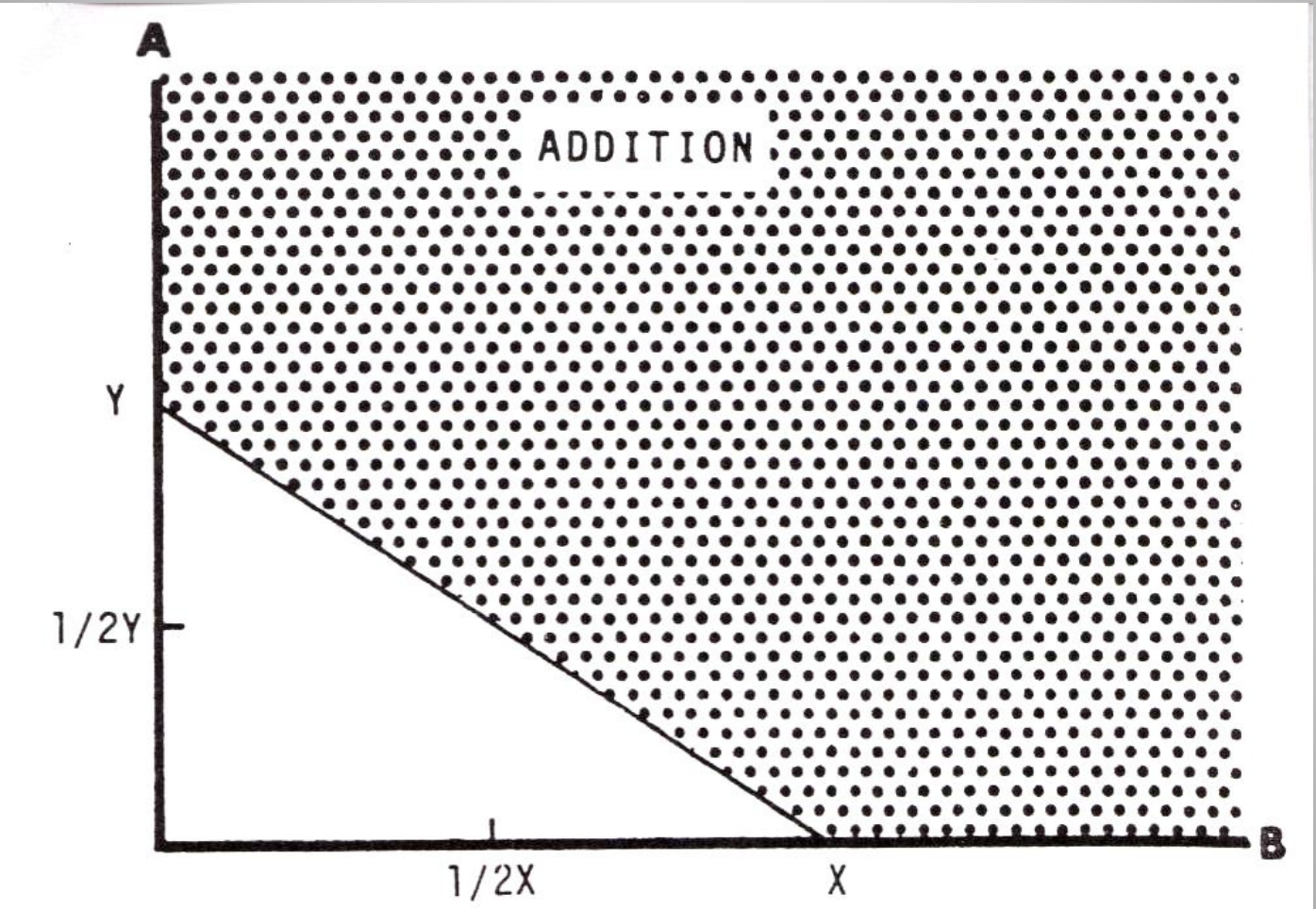
# European LTG Conversion to Monotherapy Study

Table 5
Mean seizure reduction and lamotrigine doses and concentrations

| | *n* | Seizure reduction (%) | LTG dose (mg/day) | LTG concentration (mg/l) |
|---|---|---|---|---|
| Valproate | | | | |
| Add-on | 115 | 83 | 96 | 4.7 |
| Withdrawal | 57 | 83 | 120 | 4.1 |
| Monotherapy | 36 | 60 | 204 | 5.5 |
| Carbamazepine | | | | |
| Add-on | 129 | 43 | 347 | 3.6 |
| Withdrawal | 50 | 57 | 378 | 4.9 |
| Monotherapy | 28 | 77 | 373 | 8.2 |
| Phenytoin | | | | |
| Add-on | 92 | 34 | 359 | 3.3 |
| Withdrawal | 31 | 60 | 389 | 5.2 |
| Monotherapy | 16 | 80 | 397 | 6.7 |

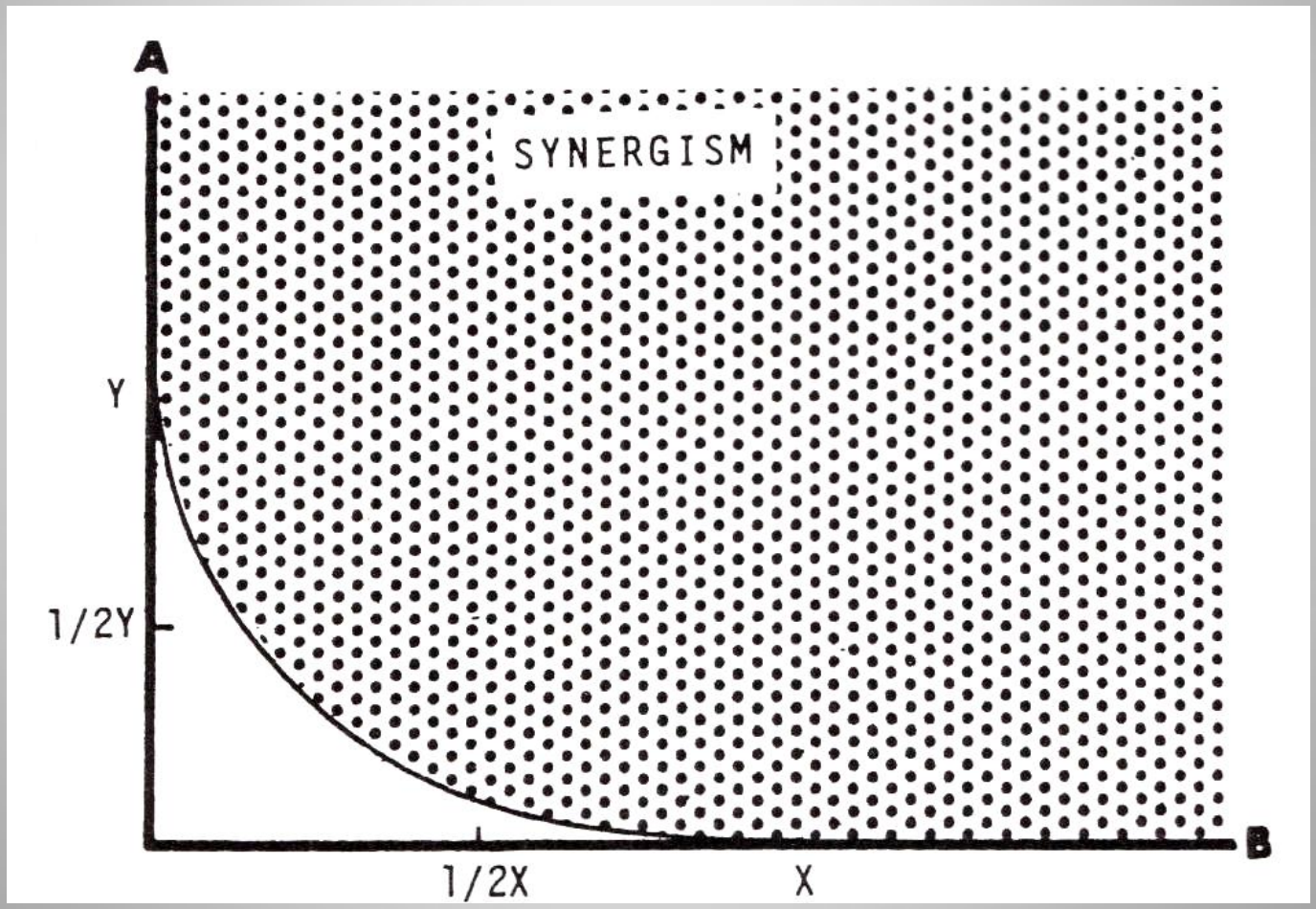
*M.J. Brodie*, *A.W.C. Yuen* : *Epilepsy Research* 26 (1997) 423–432

# Isobologram showing addition between drugs X and Y



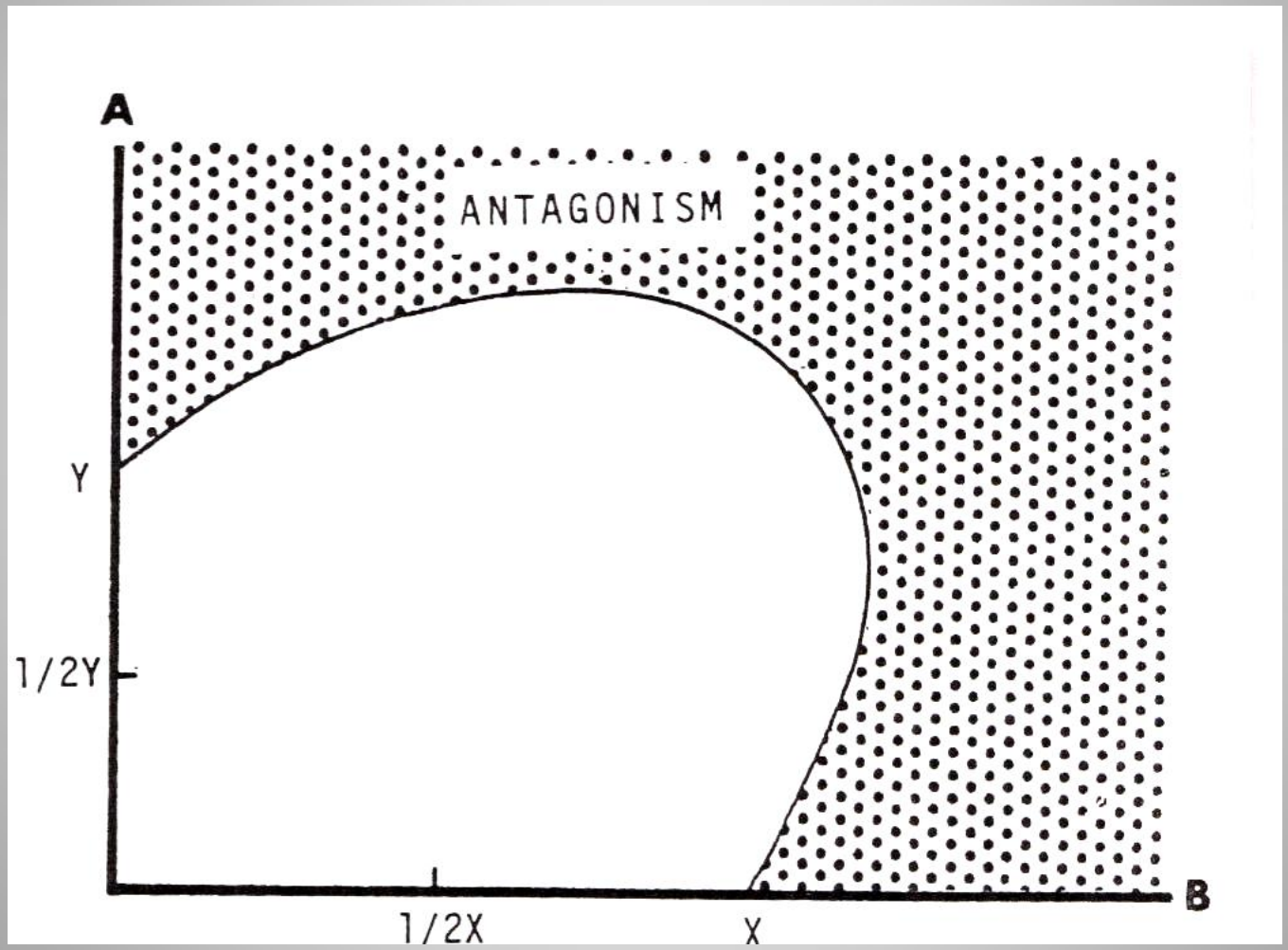

Masuda et al., 1981

# Isobologram showing synergism between drugs X and Y



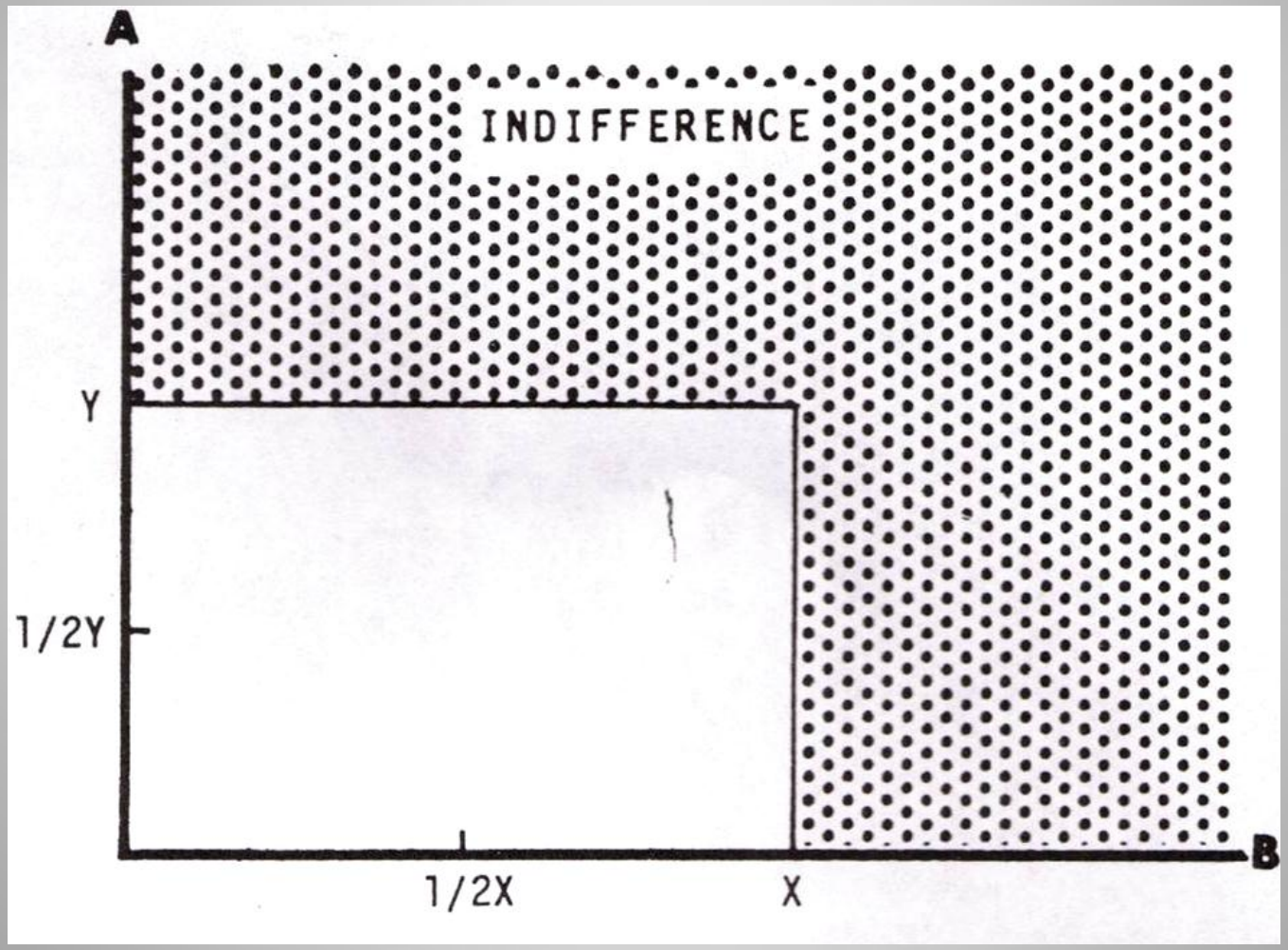

Masuda et al., 1981

# Isobologram showing antagonism between drugs X and Y



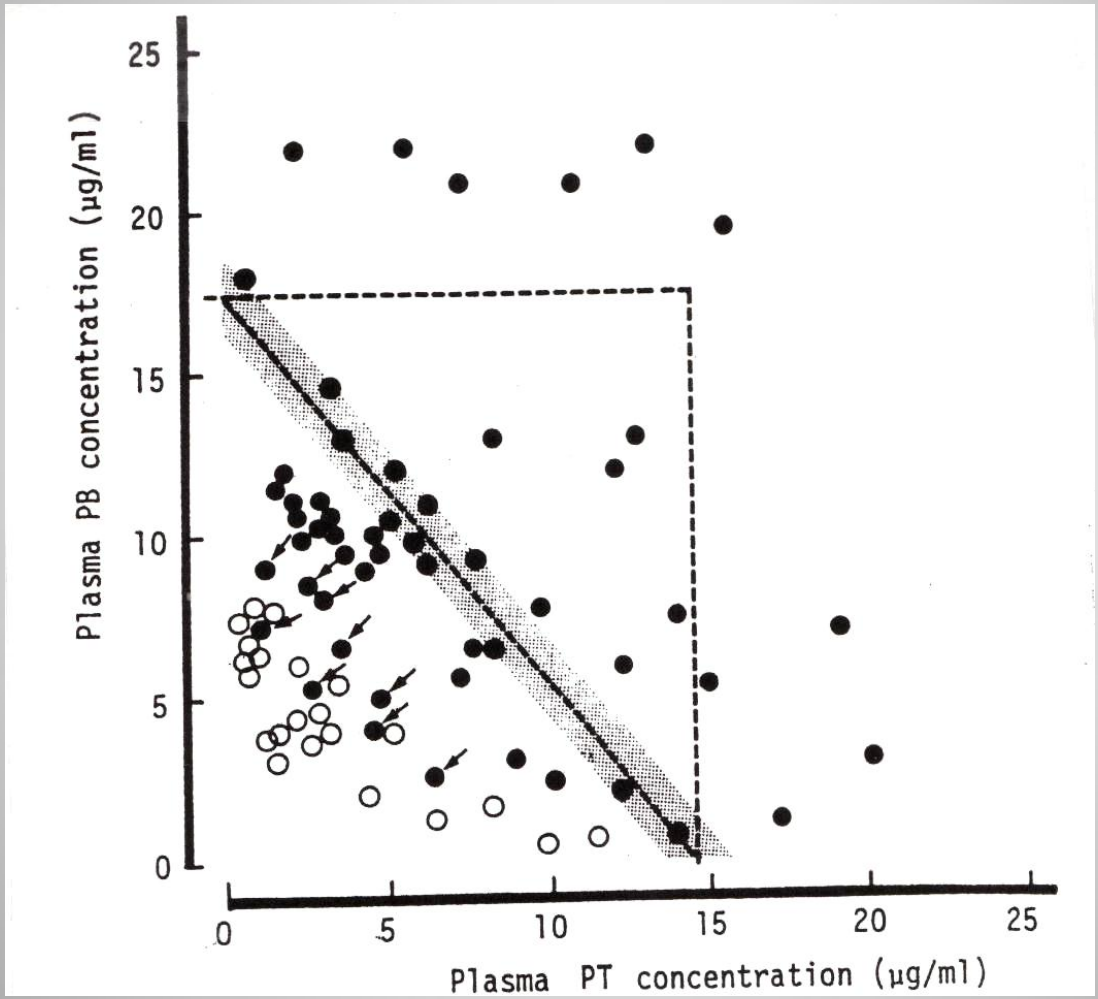

Masuda et al., 1981

# Isobologram showing no interaction between drugs X and Y



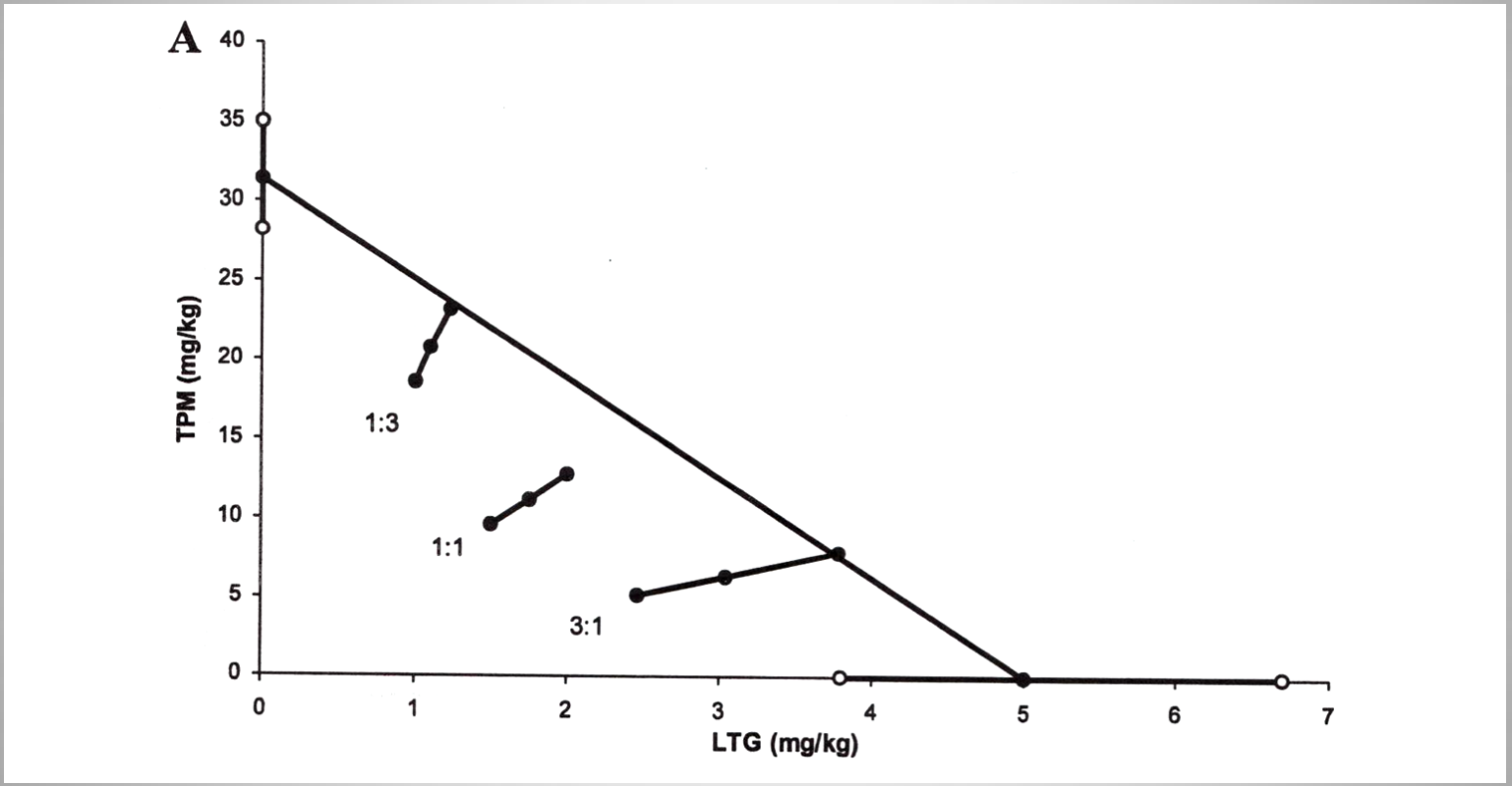

Masuda et al., 1981

# Isobologram showing synergism between drugs PHT and PB



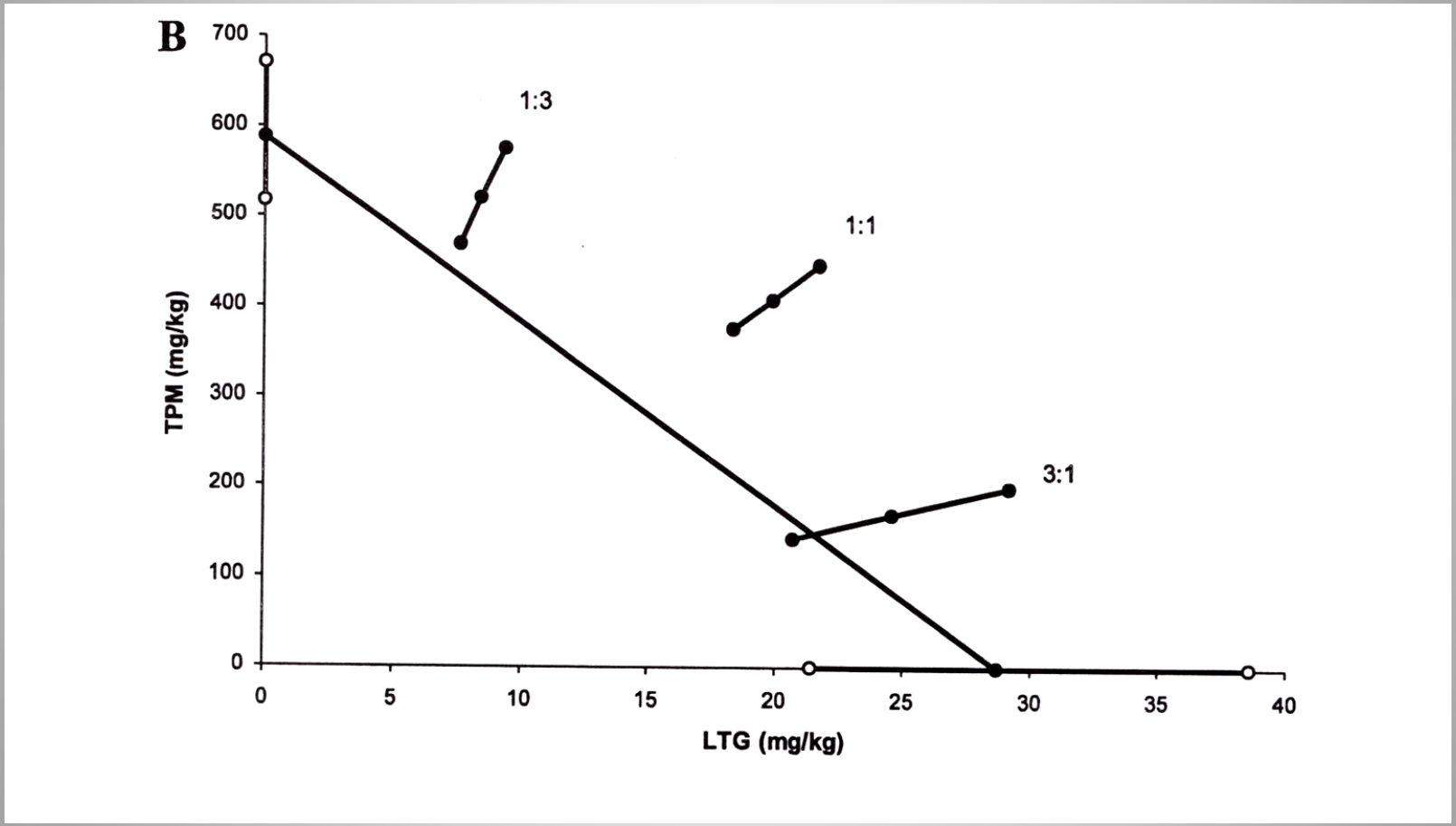

Masuda et al., 1981

# Isobologram showing synergism of efficacy between LTG and TPM




Czuczwar & Borowicz, 2002

# Isobologram showing antagonism of neurotoxicity between LTG and TPM




Czuczwar & Borowicz, 2002

# Common Side Effects and Idiosyncratic Reactions of AEDs

# AEDs and Idiosyncratic Reactions

**TABLE 65-5** Antiepileptic Drug Side Effects

| Antiepileptic Drug | Concentration Dependent | Idiosyncratic | Chronic Side Effects |
|---|---|---|---|
| Carbamazepine | Diplopia<br>Dizziness<br>Drowsiness<br>Nausea<br>Unsteadiness<br>Lethargy | Blood dyscrasias<br>Rash | Hyponatremia |
| Ethosuximide | Ataxia<br>Drowsiness<br>GI distress<br>Unsteadiness<br>Hiccoughs | Blood dyscrasias<br>Rash | Behavior changes<br>Headache |
| Felbamate | Anorexia<br>Nausea<br>Vomiting<br>Insomnia<br>Headache | Aplastic anemia<br>Acute hepatic failure | Not established |

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# AEDs and Idiosyncratic Reactions

**TABLE 65-5** Antiepileptic Drug Side Effects

| Antiepileptic Drug | Concentration Dependent | Idiosyncratic | Chronic Side Effects |
|---|---|---|---|
| Gabapentin | Dizziness<br>Fatigue<br>Somnolence<br>Ataxia | Pedal edema | Weight gain |
| Lacosamide | Dizziness<br>Headache<br>Nausea<br>Vomiting<br>PR interval increase on ECG | Liver enzyme elevation | Not established |
| Lamotrigine | Diplopia<br>Dizziness<br>Unsteadiness<br>Headache | Rash | Not established |
| Levetiracetam | Sedation<br>Behavioral disturbance | Psychosis (rare) | Not established |

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# AEDs and Idiosyncratic Reactions

**TABLE 65-5** Antiepileptic Drug Side Effects

| Antiepileptic Drug | Concentration Dependent | Idiosyncratic | Chronic Side Effects |
|---|---|---|---|
| Oxcarbazepine | Sedation<br>Dizziness<br>Ataxia<br>Nausea | Rash | Hyponatremia |
| Phenobarbital | Ataxia<br>Hyperactivity<br>Headache<br>Unsteadiness<br>Sedation<br>Nausea | Blood dyscrasias<br>Rash | Behavior changes<br>Connective tissue disorders<br>Intellectual blunting<br>Metabolic bone disease<br>Mood change<br>Sedation |
| Phenytoin | Ataxia<br>Nystagmus<br>Behavior changes<br>Dizziness<br>Headache<br>Incoordination<br>Sedation<br>Lethargy<br>Cognitive impairment<br>Fatigue<br>Visual blurring | Blood dyscrasias<br>Rash<br>Immunologic reaction | Behavior changes<br>Cerebellar syndrome<br>Connective tissue changes<br>Skin thickening<br>Folate deficiency<br>Gingival hyperplasia<br>Hirsutism<br>Coarsening of facial features<br>Acne<br>Cognitive impairment<br>Metabolic bone disease<br>Sedation |

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# AEDs and Idiosyncratic Reactions

**TABLE 65-5** Antiepileptic Drug Side Effects

| Antiepileptic Drug | Concentration Dependent | Idiosyncratic | Chronic Side Effects |
|---|---|---|---|
| Pregabalin | Dizziness<br>Somnolence<br>Blurred vision | Pedal edema<br>Creatine kinase elevation<br>Decrease platelets | Weight gain |
| Primidone | Behavior changes<br>Headache<br>Nausea<br>Sedation<br>Unsteadiness | Blood dyscrasias<br>Rash | Behavior change<br>Connective tissue disorders<br>Cognitive impairment<br>Sedation |
| Rufinamide | Dizzness<br>Nausea<br>Vomiting<br>Somnolence | Multiorgan hypersensitivity<br>Status epilepticus<br>Leukopenia<br>QT shortening | Not established |
| Tiagabine | Dizziness<br>Fatigue<br>Difficulties concentrating<br>Nervousness<br>Tremor<br>Blurred vision<br>Depression<br>Weakness | Spike-wave stupor | Not established |

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# AEDs and Idiosyncratic Reactions

**TABLE 65-5** Antiepileptic Drug Side Effects

| Antiepileptic Drug | Concentration Dependent | Idiosyncratic | Chronic Side Effects |
|---|---|---|---|
| Topiramate | Difficulties concentrating<br>Psychomotor slowing<br>Speech or language problems<br>Somnolence, fatigue<br>Dizziness<br>Headache | Metabolic acidosis<br>Acute angle glaucoma<br>Oligohydrosis | Kidney stones<br>Weight loss |
| Valproic acid | GI upset<br>Sedation<br>Unsteadiness<br>Tremor<br>Thrombocytopenia | Acute hepatic failure<br>Acute pancreatitis<br>Alopecia | Polycystic ovary–like syndrome<br>Weight gain<br>Hyperammonemia<br>Menstual cycle irregularities |
| Vigabatrin | Permanent vision loss<br>Fatigue<br>Somnolence<br>Weight gain<br>Tremor<br>Blurred vision | Abnormal MRI brain signal changes (infants with infantile spasms)<br>Peripheral neuropathy<br>Anemia | Permanent vision loss |
| Zonisamide | Sedation<br>Dizziness<br>Cognitive impairment<br>Nausea | Rash<br><br>Oligohydrosis | Kidney stones<br>Weight loss |

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# AEDs and Co-Morbidites

# AEDs and Co-Morbidities

- Check for Drug interactions
  - Enzyme Inducing AEDs (i.e.: Phenytoin) do not mix well with drugs for HIV, cholesterol, chemotherapy, calcium channel drugs, etc.
- Check for Chronic Reactions
  - Gabapentin and Valproate increase weight; perhaps not best AEDs in an obese diabetic

# Conclusions

**Understanding the Pharmacology of AEDs helps:**

- Identifying drug interactions of AEDs,
- Combining AEDs more effectively,
- Educating patients about common side effects of AEDs and identifying early idiosyncratic reactions, and
- Predicting common effects of AEDs on co-morbidities.