Antiepileptic Drugs (AEDs): Current Concepts

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Goals of AED Therapy

Sz Control without Adverse Effects

- Accurate dx
  - Sz classification
  - Epilepsy classification (1°/2°)
- Specific drug for sz/epilepsy type

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Considerations When Using AEDs

- Start with single drug
- Select AED specific for seizure type
- Optimize AED
  - Balance seizure control vs toxicity
- Anticipate drug interactions
- Polypharmacy only after monotherapy fails
  - *When to add?*
  - *How to add?*
  - *What to add?*

Established Drugs for Partial Seizures

- Carbamazepine
- Phenytoin
- Valproic acid
- Phenobarbital
- Primidone

Which AEDs to Use:
Partial Seizures w/wo GTCS

Drugs of choice
- CBZ
- PHT

Second line AEDs
- VPA
- PB
- PRM

Newer AEDs
- LTG
- TPM
- OXC
- LEV
- ZNS
- PGB
- LCM

Second line AEDs
- GBP
- TGB

Established Drugs for Generalized Seizures

Tonic-Clonic	Absence	Myoclonic
■ Carbamazepine	■ Ethosuximide	■ Valproic acid
■ Phenytoin	■ Valproic acid	■ Clonazepam
■ Valproic acid		■ Other benzodiazepines
■ Primidone		
■ Phenobarbital		

Which AEDs to Use:
Primary Generalized Epilepsy

Drugs of choice

- Simple absence (CAE)
  - VPA
  - ESM
- GTCS
  - VPA
  - CBZ
  - PHT
- Mixed PGE
  - VPA

Newer AEDs

- LTG
- TPM
- LEV
- ZNS

Reasons for Incomplete Seizure Control

Patient Factors

- Noncompliance
- Intercurrent illness
- Alcohol
- Sleep loss
- Stress

Diagnosis

- Misclassification
- Nonepileptic seizures

Medication

- Wrong AED for seizure type
- Drug interactions
- Inadequate dose
- Polypharmacy

Initiating AED Therapy

Safety Monitoring

- Blood chemistries, hemat eval, liver function studies
  - Pretherapy
  - 6-8 wk postinitiation
- Routine monitoring not helpful
- Familiarize pt with AEs, be available for eval

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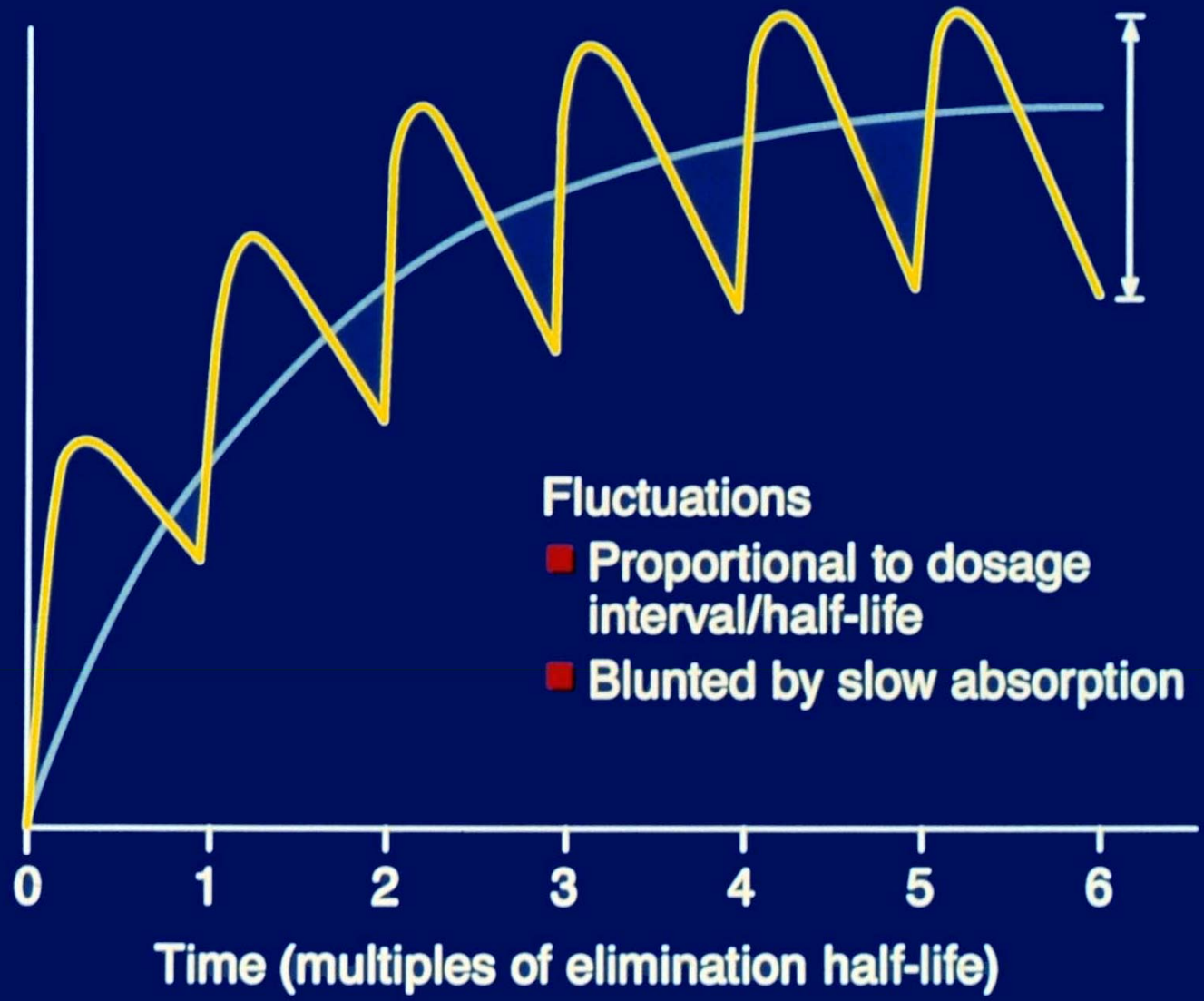
Timing of AED Adminstration



AED Monitoring

- After starting AED
  - PHT (2-3 wk)
  - CBZ (3, 6, 9 wk)
  - VPA (1 wk)
- After other drugs (starting or stopping)
- Toxicity (peak)
- Breakthrough sz (trough)
- Noncompliance (nonspecific)

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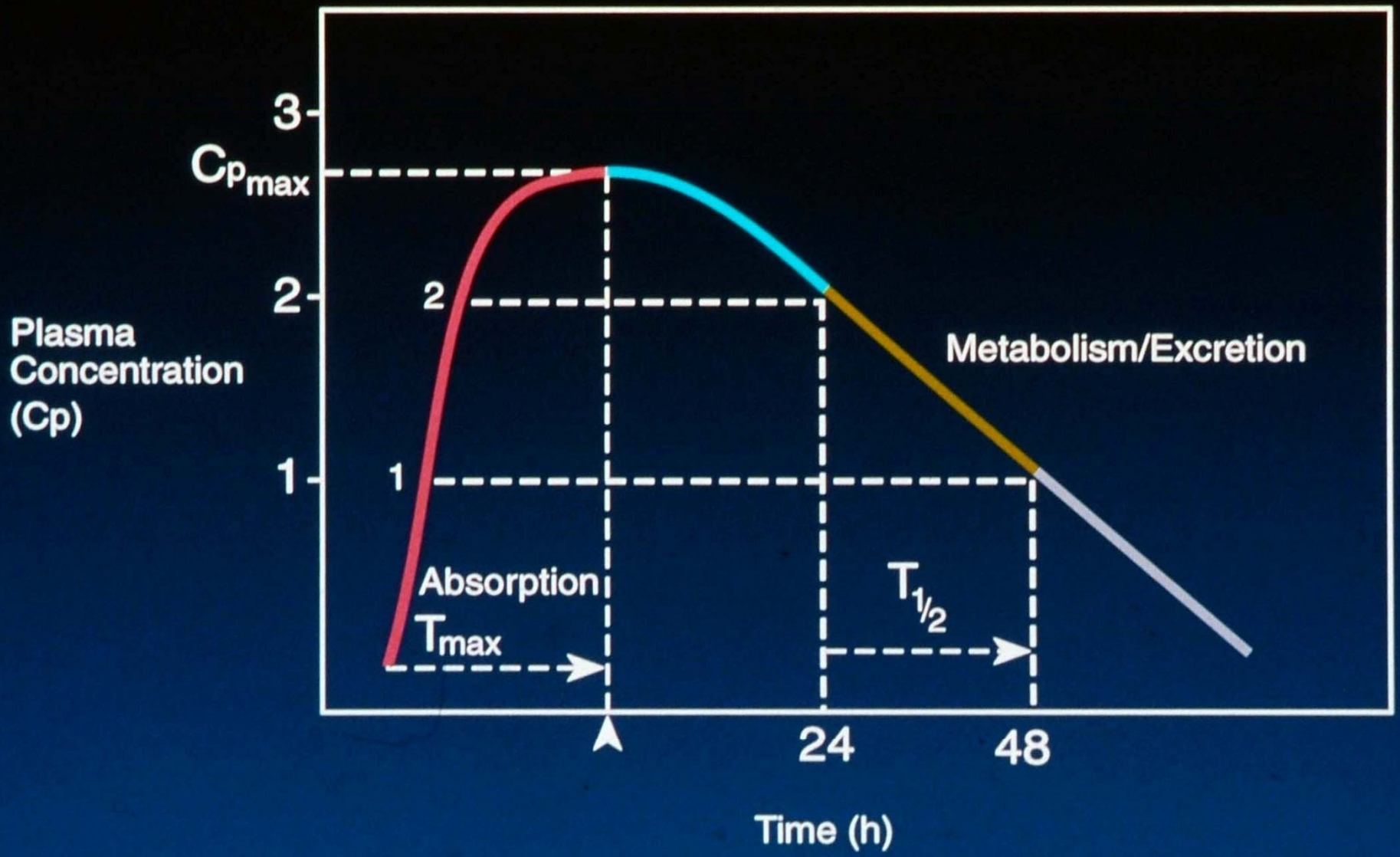
Pharmacokinetic Considerations With AEDs

Absorption

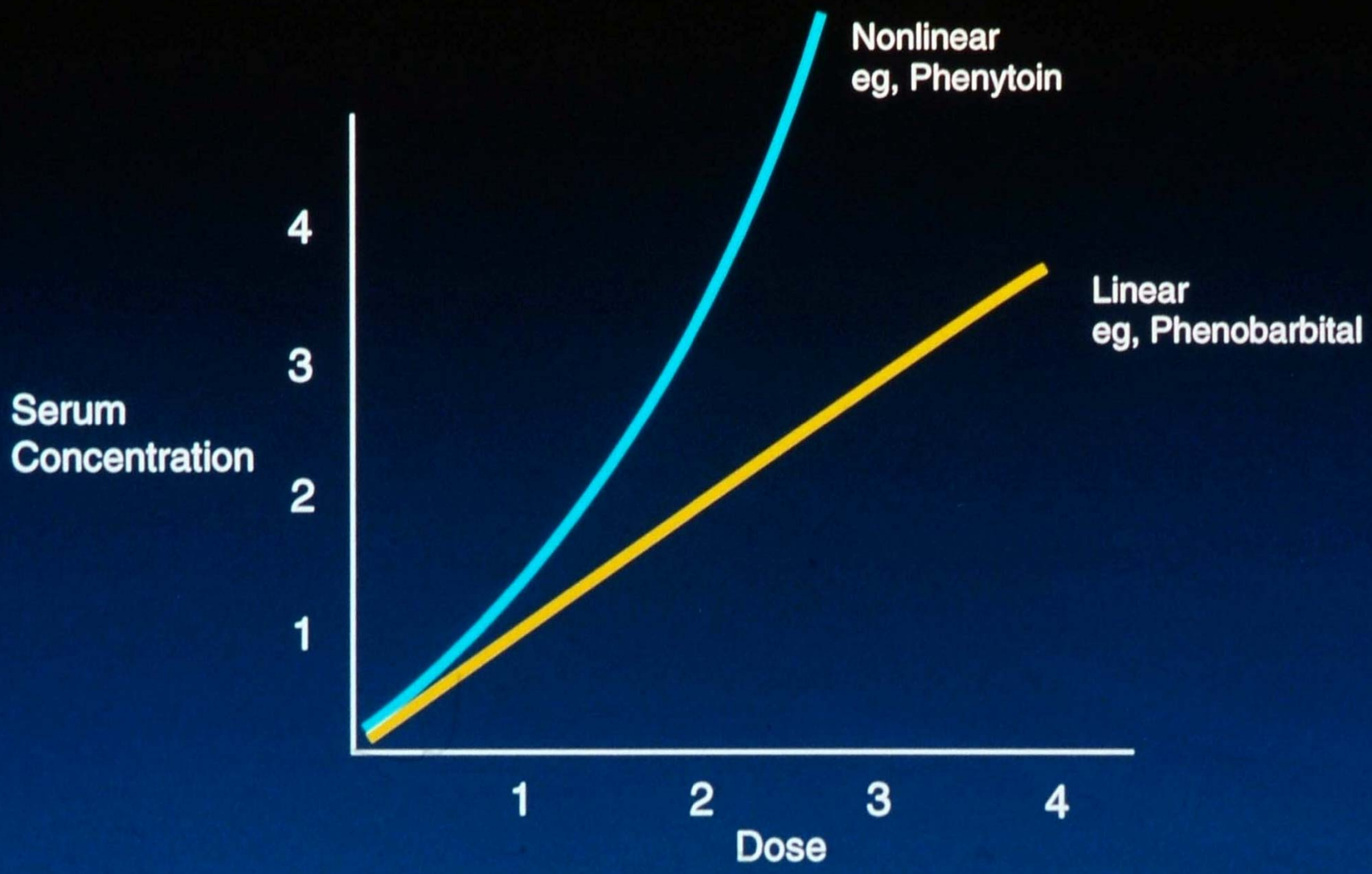
Distribution
- Volume of distribution (V_d)
- Protein binding

Metabolism/**E**xcretion
- Half-life
- Metabolites
- Drug interactions

Pharmacokinetics: Single Dose



Pharmacokinetics: Linear vs Nonlinear



Agents That Can Affect AEDs

A
Absorption Interference

- Antacids
- Some enteral feeding solutions

D
Displacers

- Aspirin (high dose)
- Valproate

M/E
Inhibitors

- Alcohol (intermittent)
- Cimetidine
- Disulfiram
- Erythromycin
- Fluoxetine
- Propoxyphene
- Valproate

Inducers

- Alcohol (chronic)
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin

Agents That Can Be Affected by AEDs

- Folic acid
- Meperidine
- Oral anticoagulants
- Oral contraceptives
- Steroids
- Theophylline
- Vitamin D
- Vitamin K

Established AEDs

Phenytoin (PHT)

- Indications: SPS, CPS, w/wo 2ary GTCS. Primary GTCS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ gum hyperplasia, hirsutism). Idiosyncratic reactions.
- Mechanism of Action: Sodium channel blocker. Decrease sustained high-frequency neuronal firing.
- Pharmacokinetics: $t_{1/2}$=24 hours. Metabolized in liver. Nonlinear kinetics. 90% protein bound.
- Drug Interactions: Decrease CBZ, PB, LTG, TPM, TGB levels. Displaces VPA, ?CBZ from albumin, increasing free levels.
- Dosing: Q day. Begin with full maintenance dose. Ultimate dose variable & based on serum drug level and response.

Carbamazepine (CBZ)

- Indications: SPS, CPS, w/wo 2ary GTCS. Primary GTCS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ diplopia, leukopenia, hyponatremia). Idiosyncratic reactions. SJS/TEN in Asians with HLA-B* 1502.
- Mechanism of Action: Sodium channel blocker. Decrease sustained high-frequency neuronal firing.
- Pharmacokinetics: $t_{1/2}$=12 hours. Metabolized in liver. Autoinduction. Active epoxide metabolite (CBZ_E). 75% protein bound.
- Drug Interactions: Decrease CBZ, PHT, PB, LTG, TPM, TGB levels. Mildly displaces VPA, PHT from albumin, increasing free levels.
- Dosing: BID-QID. Begin with 200 mg BID & increase slowly to ultimate dose based on serum drug level and response.

Valproate (VPA)

- Indications: Primary generalized epilepsy. SPS, CPS, w/wo 2ary GTCS. Add-on & monotherapy.
- Side Effects: Weight gain, tremor, alopecia, GI upset. Idiosyncratic liver failure & pancreatitis.
- Mechanism of Action: Enhances GABA effects. Sodium channel blocker. Decrease sustained high-frequency neuronal firing. Reduce low-threshold T-calcium channel currents. Others.
- Pharmacokinetics: $t_{1/2}$=12 hours. Metabolized in liver. Inhibits liver enzymes. Active metabolites. 90% protein bound.
- Drug Interactions: Displaces PHT, ?CBZ from albumin, increasing free levels. Increases LTG levels. Mildly decreases TPM levels.
- Dosing: BID-QID. Begin with 15 mg/kg/day. Increase slowly to ultimate dose based on serum drug level and response (30-60 mg/day).

Phenobarbital (PB)

- Indications: SPS, CPS, w/wo 2ary GTCS. Primary GTCS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ sedation, paradoxical activation in children). Idiosyncratic reactions.
- Mechanism of Action: Prolong GABA-mediated chloride channel openings. Decrease CNS excitation.
- Pharmacokinetics: $t_{1/2}$=48-118 hours (mean=72 hours). Metabolized in liver. 25-50% excreted unchanged in urine. 50% protein bound.
- Drug Interactions: Decrease CBZ, PHT, LTG, TPM, TGB levels.
- Dosing: Q day. Begin with full maintenance dose. Ultimate dose based on serum drug level and response.

Primidone (PRM)

- Indications: SPS, CPS, w/wo 2ary GTCS. Primary GTCS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ sedation). Idiosyncratic reactions.
- Mechanism of Action: Prolong GABA-mediated chloride channel openings. Decrease CNS excitation.
- Pharmacokinetics: $t_{1/2}$=12 hours. Metabolized in liver. 50% protein bound.
- Drug Interactions: Decrease CBZ, PHT, LTG, TPM, TGB levels.
- Dosing: BID-QID. Begin with 250 mg BID & increase slowly to ultimate dose based on serum drug level and response.

Ethosuximide (ESM)

- Indications: Primary generalized epilepsy (especially simple absence seizures). Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ GI upset). Idiosyncratic reactions.
- Mechanism of Action: Reduce low-threshold T-calcium channel currents. Disrupt slow rhythmic firing of thalamic neurons.
- Pharmacokinetics: $t_{1/2}$=12 hours. Metabolized in liver. 0% protein bound.
- Drug Interactions: None significant.
- Dosing: BID-QID. Begin with 250 mg BID & increase slowly to ultimate dose based on serum drug level and response. Optimal dose for children=20 mg/kg/day.

New AEDs

Felbamate (FBM)

- Indications: SPS, CPS, w/wo 2ary GTCS. ??PGE. Lennox-Gastaut syndrome (LGS). Add-on & monotherapy.
- Side Effects: Activation, anorexia, weight loss, insomnia. Idiosyncratic liver failure & aplastic anemia.
- Mechanism of Action: Glutamate & GABA effects. Sodium & calcium channel blocker.
- Pharmacokinetics: $t_{1/2}$=24 hours. 50% metabolized in liver. Competes with other AEDs for liver enzymes. 25% protein bound.
- Drug Interactions: Decrease CBZ_T. Increase CBZ_E (50%), PHT (25-50%), VPA (25-50%) levels.
- Dosing: BID-TID. Begin with 600 mg BID & increase slowly to ultimate dose based on side effects and response. Usual dose=1200-3600 mg/day.

Gabapentin (GBP)

- Indications: SPS, CPS, w/wo 2ary GTCS. Add-on therapy.
- Side Effects: Usual AED AEs.
- Mechanism of Action: Binds to α_2-δ subunit of voltage-gated calcium channels and modulates calcium currents; thereby decreasing excitatory neurotransmitter (glutamate, NE, substance P) release.
- Pharmacokinetics: $t_{1/2}$=5-7 hours. Not metabolized in liver. Excreted in urine. Minimal protein binding. Nonlinear: Decreased absorption at higher doses.
- Drug Interactions: None.
- Dosing: TID-QID. Begin with 300 mg TID & increase slowly to ultimate dose based on side effects and response. Usual dose=1200-3600 (4800) mg/day.

Lamotrigine (LTG)

- Indications: SPS, CPS, w/wo 2ary GTCS. PGE (GTCS). LGS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ rash, especially with VPA).
- Mechanism of Action: Inhibits voltage-sensitive sodium channels & modulates presynaptic release of glutamate. Calcium channel blocker.
- Pharmacokinetics: $t_{1/2}$=12 hours (EIAED), 24 hours (monoRx, EIAED + VPA), 48 hours (VPA). Metabolized in liver. 55% protein bound.
- Drug Interactions: LTG does not affect other AED levels. EIAEDs decrease LTG (40%). VPA increases LTG (200%).
- Dosing: BID. **VPA:** 25 mg QOD x 2 wks., 25 mg/d x 2wks., slowly increase to 100-150 mg/day. **No VPA:** 50 mg/d x 2 wks., 100 mg/d x 2 wks., slowly increase to ultimate dose based on side effects and response. Usual dose=300-700 mg/day.

Topiramate (TPM)

- Indications: SPS, CPS, w/wo 2ary GTCS. PGE (GTCS). LGS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ psychomotor slowing, speech difficulties, renal stones, paresthesias, angle-closure glaucoma).
- Mechanism of Action: Unknown. Perhaps sodium channel blocker, GABA receptor activation, AMPA receptor antagonist, calcium channel inhibition. Weak carbonic anhydrase inhibitor (increase fluid intake).
- Pharmacokinetics: $t_{1/2}$=20-30 hours (No EIAEDs). $t_{1/2}$=12-15 hours (EIAEDs). Low (30-50%) liver metabolism. Excreted in urine. 15% protein bound.
- Drug Interactions: TPM does not affect other AED levels (occasional increase in PHT level). EIAEDs decrease TPM (40%).
- Dosing: BID. Begin with 25 mg/d & increase slowly to ultimate dose based on side effects and response. Usual dose=100-400 mg/day.

Tiagabine (TGB)

- Indications: SPS, CPS, w/wo 2ary GTCS. Add-on therapy.
- Side Effects: Usual AED AEs (+ fatigue, nervousness, tremor, depression, aphasia, weakness).
- Mechanism of Action: Blocks reuptake of GABA into presynaptic neuron & glia, thereby extending GABA effects on postsynaptic neuron.
- Pharmacokinetics: $t_{1/2}$=4-7 hours (EIAEDs), 7-9 hours (noninduced). Metabolized in liver (cytochrome P450 system). 90% protein bound.
- Drug Interactions: TGB does not affect other AED levels. EIAEDs decrease TGB levels.
- Dosing: BID-QID. Begin with 4-8 mg/d & increase slowly by 4-8 mg/wk to ultimate dose based on side effects and response. Usual dose=32-56 mg/day.

Oxcarbazepine (OXC)

- Indications: SPS, CPS, w/wo 2ary GTCS. Add-on & monotherapy.
- Side Effects: Usual AED AEs (+ diplopia, hyponatremia).
- Mechanism of Action: Sodium channel blocker. Decrease sustained high-frequency neuronal firing. Also, increased potassium conductance & modulation of some calcium channels.
- Pharmacokinetics: $t_{1/2}$=2 hours (OXC), 9 hours (MHD). Metabolized in liver (not by cytochrome P450) to active metabolite (MHD). Excreted in urine. 40% protein bound.
- Drug Interactions: OXC does not affect other AED levels (except increase PHT by 40% at higher doses) . EIAEDs decrease OXC (25-40%).
- Dosing: BID. Begin with 300 mg BID & increase by 600 mg/wk to ultimate dose based on side effects and response. Usual dose=1200-2400 mg/day.

Levetiracetam (LEV)

- Indications: SPS, CPS, w/wo 2ary GTCS. PGE (Myoclonic seizures in JME, GTCS). Add-on therapy.
- Side Effects: Usual AED AEs.
- Mechanism of Action: Unknown. Perhaps N-type calcium channel blocker, enhances $GABA_A$ inhibition, decreases excitation by blocking potassium rectifier current, prevents hypersynchronization of burst firing & seizure propagation in HF. Binds to synaptic vesicle protein 2A (SV2A).
- Pharmacokinetics: $t_{1/2}$=6-8 hours. Not metabolized in liver. Excreted in urine. <10% protein bound.
- Drug Interactions: None.
- Dosing: BID. Begin with 500 mg BID & increase by 500 mg/wk to ultimate dose based on side effects and response. Usual dose=1000-3000 mg/day.

Zonisamide (ZNS)

- Indications: SPS, CPS, w/wo 2ary GTCS. ?? PGE, PME. Add-on therapy.
- Side Effects: Usual AED AEs (+ psychomotor slowing, speech difficulties, renal stones, paresthesias, anorexia, agitation, headache). Idiosyncratic hypersensitivity reactions to sulfonamides (rash, hepatic necrosis, leukopenia, aplastic anemia, blood dyscrasias).
- Mechanism of Action: Unknown. Perhaps sodium channel blocker, reduce low-threshold T-calcium currents, facilitates dopaminergic/serotonergic transmission. Weak carbonic anhydrase inhibitor (increase fluid consumption).
- Pharmacokinetics: $t_{1/2}$=63 hours (plasma), 105 hours (RBCs). Metabolized in liver (cytochrome P450 system). Excreted in urine. 40% protein bound.
- Drug Interactions: ZNS does not affect other AED levels. EIAEDs decrease ZNS levels.
- Dosing: Q day-BID. Begin with 100 mg/d & increase by 100 mg Q 2 wks to ultimate dose based on side effects and response. Usual dose=100-400 (600) mg/day.

Pregabalin (PGB)

- Indications: SPS, CPS, w/wo 2ary GTCS. Add-on therapy.
- Side Effects: Usual AED AEs.
- Mechanism of Action: Binds to α_2-δ subunit of voltage-gated calcium channels and modulates calcium currents; thereby decreasing excitatory neurotransmitter (glutamate, NE, substance P) release.
- Pharmacokinetics: $t_{1/2}$=6 hours (pharmacodynamic $t_{1/2}$ is longer). Not metabolized in liver. Excreted in urine. No protein binding.
- Drug Interactions: None.
- Dosing: BID-TID. Begin with 150 mg/day & increase slowly to ultimate dose based on side effects and response.
  Usual dose=150-600 mg/day.

Lacosamide (LCM)

- Indications: SPS, CPS, w/wo 2ary GTCS. Add-on therapy.
- Side Effects: Usual AED AEs (dizziness, headache, diplopia, sedation, ataxia, diminished coordination, nystagmus, nausea, vomiting). Small increase in median PR interval (5-9 msec) on EKG.
- Mechanism of Action: Unknown. Enhances slow inactivation of sodium channels (stabilizes hyperexcitable neurons, inhibits repetitive neuronal firing). Binds to collapsin response mediator protein (CRMP-2).
- Pharmacokinetics: $t_{1/2}$=13 hours. Metabolized in liver (CYP2C19) to an inactive metabolite. Excreted in urine. <15% protein bound.
- Drug Interactions: LCM does not significantly affect other AED levels. EIAEDs decrease LCM (15-20%).
- Dosing: BID. Begin with 50 mg/day & increase slowly to ultimate dose based on side effects and response. Usual dose=200-400 mg/day.

Vigabatrin (VGB)

- Indications: Refractory SPS, CPS, w/wo 2ary GTCS. Add-on therapy (Adults). Infantile spasms in children. Monotherapy.
- Side Effects: Usual AED AEs (dizziness, fatigue, sedation, tremor, blurred vision, arthralgia). (Also, anemia, weight gain, edema, neuropathy). Progressive, permanent visual field constriction in ≥30% of patients.
- Mechanism of Action: Irreversible inhibitor of GABA transaminase (GABA-T), thereby increasing GABA levels in the CNS.
- Pharmacokinetics: $t_{1/2}$=7.5 hours (duration of drug effect dependent on GABA-T resynthesis). Not metabolized in liver. Excreted in urine. No protein binding.
- Drug Interactions: None, except for a slight decrease in total PHT level
- Dosing: BID. Begin with 500 mg BID & increase by 500 mg/wk to ultimate dose based on side effects and response.
  Usual dose=1000-3000 mg/day.

AED Side Effects

Goals of Epilepsy Treatment

- Complete sz control
- No AEs

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Common AED Side Effects

CBZ	PB	PHT	VPA
Double/blurred vision	Sedation/lethargy	Nystagmus	GI upset
Vertigo	Cognitive impairment	Incoordination	Weight gain
GI upset/ diarrhea	Behavioral changes/ hyperactivity	Ataxia	Hair loss/ changes
Performance impairment	Ataxia	Gingival hyperplasia	Tremor
Salt-losing syndrome	Sleep-cycle alterations		

Idiosyncratic Reactions

- Rare
- Dose independent
- Unpredictable
- Usually appear in first 3-6 mo
- May recur
- Possibly life threatening

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AED Idiosyncratic Reactions

Reaction	CBZ	ETH	PB	PHT	VPA
Agranulocytosis	x	x	x	x	x
Stevens-Johnson	x	x	x	x	x
Aplastic anemia	x	x		x	x
Hepatic failure	x		x	x	x
Dermatitis/rash	x	x	x	x	x
Serum sickness	x	x	x	x	x
Pancreatitis	x				x

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AED Hepatotoxicity

Associated AEDs

- CBZ
- PHT
- VPA

Histopathologic reactions

- Necrosis
- Steatosis
- Hypersensitivity

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AED Hepatotoxicity: Signs and Symptoms

- Loss of appetite
- N&V
- Edema (periorbital, dependent)
- Abdominal pain
- Lethargy
- Easy bruisability
- Malaise
- Loss of sz control

VPA: Hepatic Fatality Rates

Ages (yr)	1978-84		1985-86	
	Poly	Mono	Poly	Mono
0-2	1/500	1/7,000	1/800	0
3-10	1/6,500	1/9,000	1/7,000	1/21,000
11-20	1/11,500	0	0	0
21-40	1/16,500	0	0	0
41+	1/38,000	0	0	0
Overall	1/6,500	1/37,000	1/20,000	1/118,000

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AED-Associated Pancreatitis

- Associated AEDs
  - CBZ
  - VPA
- Rare
- N&V, abdominal pain
- Can be life threatening
- Diagnosis
  - Hyperamylasemia
  - Ultrasound

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AED-Associated Skin Reactions

Types

- Exfoliative dermatitis
- Stevens-Johnson syndrome
- Lyell's syndrome

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Signs of Life-Threatening Dermatitis

Signs

- Pain
- Exfoliation
- Mucous membrane involvement
- Systemic symptoms/fever

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TABLE 3. *A selection of serious idiosyncratic reactions associated with individual AEDs*

	SJS/TEN[a]	Liver toxicity	Pancreatitis	Aplastic anemia	Agranulocytosis	Systemic lupus erythematosus
Carbamazepine	*	*	*	**	**	*
Ethosuximide	*	*	–	*	*	*
Felbamate	*	**	*	**	**	*
Gabapentin	*	*	–	–	–	–
Lamotrigine	**	*	*	*	–	–
Levetiracetam	–	*	*	–	–	–
Oxcarbazepine	*	*	–	–	–	–
Phenobarbital	*	*	–	–	*	*
Phenytoin	*	*	–	*	*	*
Pregabalin	–	–	–	–	–	–
Primidone	*	*	–	–	*	*
Tiagabine	*	–	–	–	–	–
Topiramate	*	*	*	–	–	–
Valproic acid	*	**	**	–	–	*
Vigabatrin	–	*	*	–	–	–
Zonisamide	*	*	–	*	*	–

The table is based on information sourced from Battino et al. (2000) and supplemented with information from the latest available U.S. prescribing information monographs and from the *Drug Information Monographs, Clinical Pharmacology*, Version 6.09 (updated September 2006), Gold Standard, Tampa, FL (http://cponline.hitchcock.org). For some of the reactions reported, information is insufficient to draw definitive conclusions about causality. An asterisk (*) indicates that the specified reaction has been reported for that drug. A double asterisk (**) identifies reactions associated with a warning box in the U.S. prescribing information monographs. – indicates that the reaction has not been reported based on the sources of information stated above.

[a]SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Zaccara G, et al. Epilepsia 2007;48:1223-1244

TABLE 3. *A selection of serious idiosyncratic reactions associated with individual AEDs*

	SJS/TEN[a]	Liver toxicity	Pancreatitis	Aplastic anemia	Agranulocytosis	Systemic lupus erythematosus
Carbamazepine	*	*	*	**	**	*
Ethosuximide	*	*	–	*	*	*
Felbamate	*	**	*	**	**	*
Gabapentin	*	*	–	–	–	–
Lamotrigine	**	*	*	*	–	–
Levetiracetam	–	*	*	–	–	–
Oxcarbazepine	*	*	–	–	–	–
Phenobarbital	*	*	–	–	*	*
Phenytoin	*	*	–	*	*	*
Pregabalin	–	–	–	–	–	–
Primidone	*	*	–	–	*	*
Tiagabine	*	–	–	–	–	–
Topiramate	*	*	*	–	–	–
Valproic acid	*	**	**	–	–	*
Vigabatrin	–	*	*	–	–	–
Zonisamide	*	*	–	*	*	–

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TABLE 4. *Management of AED-induced immune-mediated idiosyncratic reactions*

- Prompt recognition of the reaction and withdrawal of the offending drug are essential management steps.
- Most patients need a complete blood count and biochemistry (including thyroid function tests) for the evaluation of internal organ involvement. Such tests should be repeated at 3 months. Additional investigations (e.g., chest radiograph, bone marrow or skin biopsy) may be indicated depending on clinical presentation.
- Patients with drug rash with eosinophilia and systemic symptoms (DRESS) require hospitalization for symptomatic and supportive therapy. Patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) should be preferentially managed in burn units.
- Treatment with corticosteroids is advisable, controversial or contraindicated, depending on the condition. Other treatments (e.g., immunoglobulins, immunosuppressants, organ transplantation, etc.) should be considered depending on clinical presentation.
- An appropriate AED should replace the withdrawn AED, to prevent recurrence of seizures and status epilepticus. AEDs expected to be involved in cross-reactivity reactions or to aggravate the underlying pathology should be avoided.
- Patients with serious hypersensitivity reactions should not be rechallenged. The value of patch tests and in vitro tests for assessing causality and predicting risk of recurrence is limited.

Zaccara G, et al. Epilepsia 2007;48:1223-1244

Topiramate (TPM): Angle-closure glaucoma

- Occurs more often in females. Younger age than in the usual patient with glaucoma.
- Occurs within 3 weeks of initiation of TPM treatment
- Occurs at low doses (50-150 mg/d)
- Symptoms: Acute blurred vision (due to acute myopia), pain, and redness in both eyes
- Caused by choroid and ciliary body swelling which "pushes" the angle of the anterior chamber closed
- Stopping TPM is the only effective treatment