Therapy of Epilepsy

Therapy of Epilepsy

- **Epilepsy is a common neurologic condition in which a person is prone to recurrent epileptic seizures.**
- **There are many types of epilepsies characterized by different seizure types, with differences in severity and etiologies.**
- **In all epilepsies, there is disrupted regulation of electrical activity in the brain resulting in synchronized and excessive neuronal discharge.**

Therapy of Epilepsy

- **Accurate classification and diagnosis of seizure type, including mode of seizure onset, is critical to selection of appropriate pharmacotherapy.**

Therapy of Epilepsy

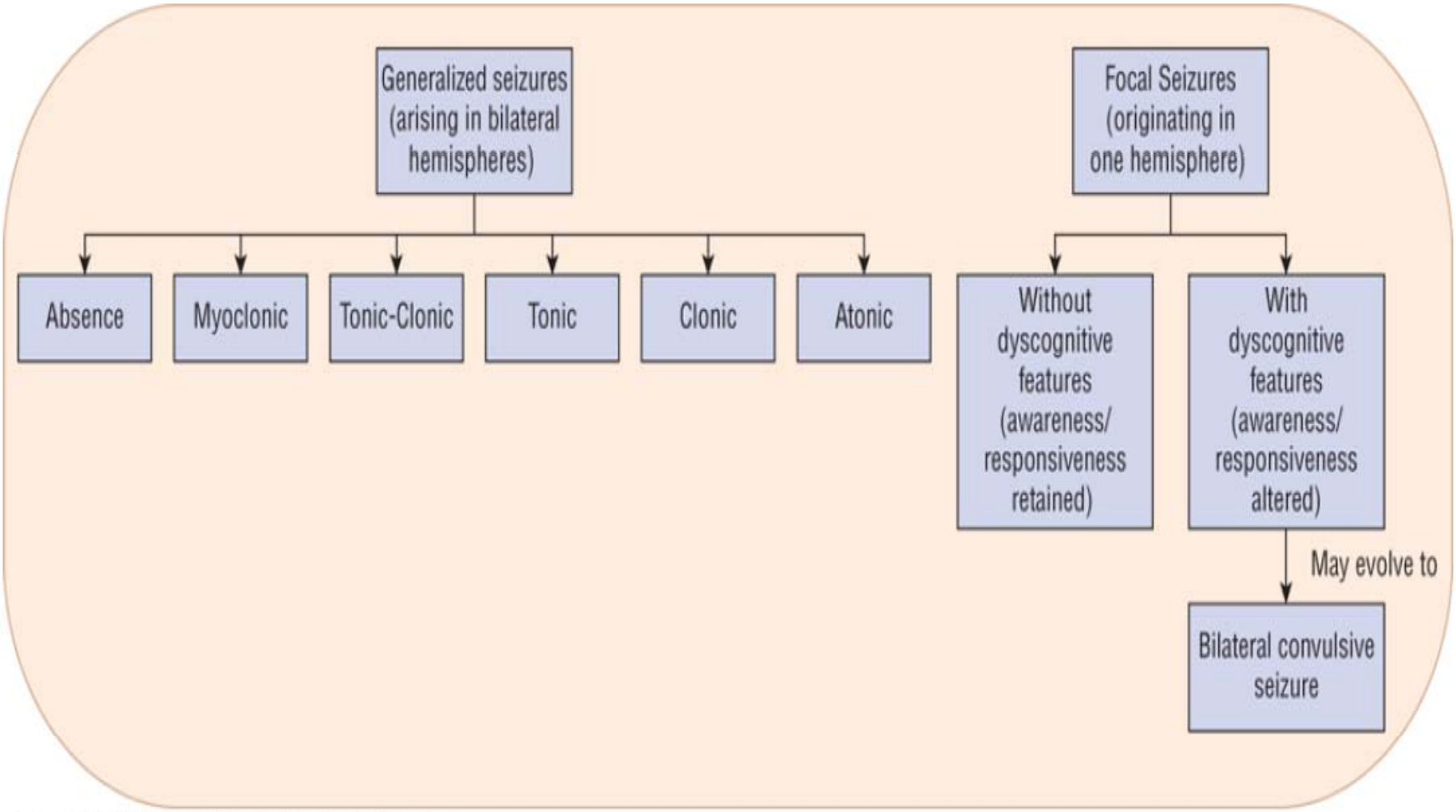
Aims of Drug therapy:

a) **Reduce the frequency of seizures as much as possible.**
b) **Minimizing adverse drug effects.**
c) **Addressing coexisting health and social conditions.**
d) **Enhancing quality of life (QOL).**

Therapy of Epilepsy

- **Some seizures are provoked by infections; fever (febrile seizures); drug overdose; alcohol, barbiturate or benzodiazepine withdrawal; brain hemorrhage; or (hypocalcemia, hypoglycemia, uremia, and eclampsia).**
- **These seizures do not constitute epilepsy, they disappear once the provoking insult is removed or treated.**

2010 ILAE Revised Terminology for Classification of Seizures.



Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic Approach, 10th Edition, www.accesspharmacy.com

Therapy of Epilepsy

Treatment:

- **Anti-seizure drug (ASD) therapy is the mainstay of epilepsy treatment.**
- **ASDs are symptomatic treatment only.**
- **They have no disease modifying properties, and are not curative.**
- **Drugs act to prevent seizures mainly.**
- **Therapy is usually life-long.**

Therapy of Epilepsy

- **Remember that the goal of ASD therapy is to eliminate seizures with minimal adverse effects.**
- **In 20% to 35% of patients this may not be possible, and seizure control must be balanced with QOL goals.**
- **For those who can NOT obtain seizure freedom despite these therapies, a decrease in the number of seizures with minimized drug adverse effects will be a reasonable goal.**

Therapy of Epilepsy

If the therapeutic goal is not achieved with monotherapy:

1. **Add a second antiseizure drug (ASD), preferably with a different mechanism of action.**
2. **Or switch to an alternative single ASD.**

- **Emphasize treatment with a single drug!!**

Therapy of Epilepsy

- **The drug treatment of first choice depends on the type of epilepsy; and patient characteristics such as age, gender, co-morbid medical conditions, susceptibility to adverse effects, ability to comply with a prescribed regimen.**
- **Polytherapy should be considered in patients who cannot achieve seizure freedom on monotherapy.**

Therapy of Epilepsy

- **Once the proper ASD is selected, patient education and understanding of the treatment plan is essential.**

➢ **The single most common reason for treatment failure is medication non-adherence.**

- **Up to 60% of patients with epilepsy are non-adherent.**
- **Financial constraints can lead to non-adherence.**

Therapy of Epilepsy

- **The rate of non-adherence is increased by the complexity of the drug regimen (such as doses taken 3-4 times a day).**
- **Frequent uncontrolled seizures can lead to non-adherence because of confusion over whether the drug was taken or not.**

➢ **Anti-seizure drug withdrawal should be gradual, to avoid recurrence of seizures. Sudden withdrawal can be associated with "Status Epilepticus".**

Therapy of Epilepsy

- **Withdrawal seizures are more common with benzodiazepines and barbiturates, which should be withdrawn more slowly over a period of many months.**

Therapy of Epilepsy

Pharmacologic Therapy:

- **An ASD must be effective for the specific seizure type.**
- **Individualization of therapy is important.**
- **A patient may be better suited to receive one drug over the other, because of susceptibility for certain adverse effects.**
- **Patient characteristics such as age, gender, medical conditions must be considered:**

Therapy of Epilepsy

- **Children may be more susceptible to neuropsychiatric adverse effects.**
- **Women of child-bearing potential should not receive teratogenic drugs.**
- **The elderly may be more susceptible to adverse effects on cognition, therefore, avoid drugs that affect cognition.**

Therapy of Epilepsy

- **Patients with co-morbid conditions (migraine headache, tremor, or neuropathy) may benefit from the use of particular drug that can also treat the other condition.**
- **** Extreme attention should be paid to drug-drug interactions with other drugs, and among ASDs themselves!!!**

Therapy of Epilepsy

1. **Select one ASD, start with a low dose, and gradually titrate to a moderate dose goal, taking into account the patient's response to treatment.**

- **If the patient is seizure free with no adverse effects at a moderate therapeutic dose, then no further increase in dose is necessary.**

2. **If there is no adequate response at that dose, attempt increasing the dose.**

Therapy of Epilepsy

3. **If the first ASD monotherapy is still ineffective, or if the patient experiences intolerable adverse effects, adding a second ASD with a different mechanism of action and then tapering and discontinuing the first ASD is appropriate.**
4. **If the second ASD is ineffective, combination therapy may be indicated (although it is not desirable).**

Therapy of Epilepsy

- **In elderly patients who are sensitive to falls, sedation, and neuro-cognitive adverse effects, start at much lower initial doses and then titrate slowly (weeks – months), with a lower maximum dose goal.**
- **In patients with multiple recent seizures, a therapeutic dose needs to be reached much more quickly, and a more rapid titration over days instead of weeks is appropriate.**

Therapy of Epilepsy

Effectiveness of ASDs:

- **Some ASDs including carbamazepine, ethosuximide, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproic acid, and zonisamide, have strong enough evidence to be labeled as effective, or as probably effective as initial monotherapy in certain seizure types.**
- **Others have weaker evidence and can only be labeled as possibly or potentially effective.**

Therapy of Epilepsy

Drug Resistance:

- **Drug resistance is defined as "failure of two tolerated and appropriately chosen ASD schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom."**
- **Approximately 65% of patients can be maintained on one ASD and considered well controlled, although not necessarily seizure free.**

Therapy of Epilepsy

- **The percentage of patients who are seizure-free on one drug after 12 months of treatment varies:**

a) **For those who have only generalized tonic-clonic seizures (~ 50 %).**

b) **For those who have only focal seizures (~ 25%).**

c) **For those with mixed seizure types (~ 25%).**

Therapy of Epilepsy

- **Of the 35% of patients with unsatisfactory control on monotherapy, 10% will be well controlled with a two-drug combination.**
- **Of the remaining 25%, 20% will continue to have unsatisfactory control despite greater than two drug treatment and are considered drug-resistant.**

Therapy of Epilepsy

Pharmacokinetics and Drug-Drug Interactions:

- **Selection of an appropriate drug requires Knowledge about pharmacokinetic variability of the drug.**
- **Knowledge of ASD inducer or inhibitory effects on drug metabolizing enzymes is needed for the optimization of ASD therapy.**
- **Pharmacokinetic interactions are a common and serious complicating factor in ASD selection.**

Antiseizure Drug Inducers and Inhibitors of hepatic Enzymes

ASD	Induces	Inihibits	Metabolized by
Carbamazepine	CYP1A2; CYP2C; CYP3A; GT		CYP3A4; CYP1A2; CYP2C8
Clobazam		CYP2D6	CYP3A4; CYP2C19; CYP2B6
Felbamate	CYP3A4	CYP2C19; β - oxidation	CYP3A4; CYP2E1; other
Lamotrigine	GT		GT
Oxcarbazepine	CYP3A4; CYP3A5; GT	CYP2C19	Cytosolic system
Perampanel	CYP3A4/5;GT	CYPA3A4/5	CYP3A4/5; CYP1A2; CYP2B6
Phenobarbital	CYP3A; CYP2C; GT		CYP2C9; other
Phenytoin	CYP3A; CYP2C; GT		CYP2C9; CYP2C19
Topiramate	CYP3A (dose dependent)	CYP2C19	Not known
Valproic acid		CYP2C9; GT epoxide hydrolase	GT; β-oxidation
Vigabatrin	CYP2C9		None

Therapy of Epilepsy

- **Interactions can occur in any of the pharmacokinetic processes: absorption, distribution, metabolism, or elimination.**
- **Caution should be experienced when any ASD is added to or withdrawn from a drug regimen.**
- **Knowledge of the presence of active metabolites of drugs is important as they affect duration of action of the drug.**

Antiseizure Drug Pharmacokinetic Data

ASD	Time to Steady-State (Days)	Active Metabolite	Protein binding (%)
Carbamazepine	21-28, for completion of autoinduction	10,11-epoxide	40-90
Clobazam	7-14	N-desmethylclobazam	80-90
Eslicarbazepine	4-5	Oxcarbazepine	
Ethosuximide	6-12	--	
Ezogabine	3-4	N-acetyl metabolite	80
Felbamate	5-7	--	
Gabapentin	1-2	--	
Lacosamide	3	--	
Lamotrigine	3-15	--	
Levetiracetam	2	--	
Oxcarbazepine	2	10-hydroxycarbazepine	
Perampanel	14-21	--	95
Phenobarbital	14-21	--	
Phenytoin	7-28	--	90
Pregabalin	1-2	--	
Primidone	1-4	Phenobarbital	
Rufinamide	2	--	
Tiagabine		--	95
Topiramate	4-5	--	
Valproic acid	1-3	toxic	90-95, Saturable
Vigabatrin		--	
Zonisamide	5-15	--	

Therapy of Epilepsy

Adverse Effects:

Some common adverse effects shared by ASDs as a class:

1. **CNS adverse effects are among the most common effects of ASDs and include sedation, dizziness, blurred or double vision, difficulty with concentration, and ataxia.**
2. **Impairment of cognition, and barbiturates cause more cognitive impairment than other commonly used ASDs (in children it paradoxically causes hyperactivity).**

Therapy of Epilepsy

- In general, newer agents have less effects on cognition. (topiramate causes substantial cognitive impairment).
- These effects can be avoided by titrating the dose upward very slowly, or can be improved by decreasing the dose.
- Patients switched from polytherapy to monotherapy may also demonstrate improvement in cognition.

Therapy of Epilepsy

3. **Osteomalacia and osteoporosis:**

- **Phenytoin, phenobarbital, carbamazepine, oxcarbazepine, ~~felbamate~~, and valproic acid, may interfere with vitamin D metabolism.**
- **Patients receiving these drugs should have:**

a. **Supplemental vitamin D and calcium.**

b. **Bone mineral density testing if other risk factors for osteoporosis are present.**

Antiseizure Drug Adverse Effects and Monitoring

	Adverse Effects		
Drug	**Concentration-Dependent**	**Idiosyncratic**	**Chronic**
Carbamazepine	Diplopia Dizziness Drowsiness Nausea Unsteadiness Lethargy	Blood dyscrasias Rash (HLA antigen testing may be relevant to avoid Stevens-Johnson or toxic epidermal necrolysis)	Hyponatremia Metabolic bone disease (monitor Vit D and serum calcium)
Clobazam	Somnolence Sedation Pyrexia Ataxia	Drooling Aggression Irritability Constipation	
Ethosuximide	Ataxia Drowziness GI distress Unsteadiness Hiccoughs	Blood dyscrasias Rash	Behavioral changes Headaches
Ezogabine	Dizziness Somnelance Fatigue Confusion vertigo Tremors Blurred vision	Urinary retention QT prolongation (ECG baseline and during treatment) Euphoria	Blue gray skin discoloration Retinal abnormalities

Felbamate	Anorexia Nausea, vomiting Insomnia Headache	Aplastic anemia (follow CBC) Acute hepatic failure (follow liver enzymes)	
Gabapentin	Dizziness Fatigue Somnolence Ataxia	Pedal edema	Weight gain
Lacosamide	Dizziness Vertigo Headache Nausea, vomiting Prolongation of PR interval (ECG baseline and during treatment)	Liver enzyme elevations	

Lamotrigine	Diplopia Dizziness Unsteadiness Headache	Rash	
Levetiracetam	Sedation Behavioral disturbances	Psychosis	
Phenobarbital	Ataxia Hyperactivity (in children) Unsteadiness Headache Sedation Nausea	Blood dyscrasias Rash	Behavioral changes Connective tissue disorders Intellectual blunting Metabolic bone disease (monitor Vit D and serum calcium) Mood changes

Phenytoin	Ataxia Nystagmus Behavioral changes Dizziness Somnolence Incoordination Sedation Letargy Cognitive impairment Fatigue Blurring of vision	Blood dyscrasias Rash (HLA antigen testing may be relevant to avoid Stevens-Johnson or toxic epidermal necrolysis) Immunologic reactions	Behavioral changes Cerebellar syndrome Connective tissue changes Skin thickening Folate deficiency Gingival hyperplasia Hirsuitism Coarsening of facial features Acne Cognitive impairment Metabolic bone disease (monitor Vit D and serum calcium) Sedation
Pregabalin	Dizziness Somnolence Incoordination Dry mouth Blurring of vision	Pedal edema Creatine kinase elevation Decreased platelets	Wight gain
Tiagabine	Dizziness Fatigue Difficulty concentrating Nervousness Tremor Blurred vision Depression Weakness	Spike wave stupor	

Topimarate	Difficulty concentrating Psychomotor slowing Speech or language problems Somnolence Fatigue Dizziness Headache	Metabolic acidosis Acute glaucoma Oligohydrosis	Kidney stones Weight loss
Valproic acid	GI upset Sedation Unsteadiness Tremor Thrombocytopenia	Acute hepatic failure Acute Pancreatitis Alopecia	Polycystic ovary-like syndrome (increase incidence in females <20 years or overweight) Weight gain Hyperammonemia Menstrual cycle irregularities
Vigabatrin	Permanent vision loss Fatigue Somnolence Weight gain Tremor Blurred vision	Abnormal MRI brain signal changes (infants with infantile spasms) Peripheral neuropathy Anemia	Permanent vision loss (greater frequency, adults vs. children vs. infants)
Zonisamide	Sedation Dizziness Cognitive impairment Nausea	Rash (a sulfa drug) Metabolic acidosis Oligohydrosis	Kidney stones Weight loss

Therapy of Epilepsy

Role of Serum Concentration Monitoring:

- **Monitoring of the older ASDs is used to optimize therapy for an individual patient, but not as a therapeutic end point in itself.**
- **The serum concentration target should be interpreted in association with clinical response.**
- **Seizure control can occur before the "minimum" of the therapeutic range is achieved, and adverse effects can appear before the "maximum" of the range is achieved.**

Therapy of Epilepsy

- Some patients may need and tolerate concentrations beyond the maximum.
- Higher concentrations are needed to control focal dyscognitive seizures than to control tonic–clonic seizures.
- Serum levels can also be useful to:

a. document lack or loss of efficacy.

b. document nonadherance.

c. determine how much room there is to increase a dose based on expected toxicity.

Therapy of Epilepsy

d. patients with significant renal or hepatic dysfunction.
e. those taking multiple drugs.
f. women who are pregnant or taking oral contraceptives.

- Monitoring should be performed only at steady-state.
- Therapeutic concentration ranges have not been clearly defined for some of the second-generation ASDs.

Antiseizure Drug Pharmacokinetic Data

ASD	Time to Steady-State (Days)	Active Metabolite	Protein binding (%)
Carbamazepine	21-28, for completion of autoinduction	10,11-epoxide	40-90
Clobazam	7-14	N-desmethylclobazam	80-90
Eslicarbazepine	4-5	Oxcarbazepine	
Ethosuximide	6-12	--	
Ezogabine	3-4	N-acetyl metabolite	80
Felbamate	5-7	--	
Gabapentin	1-2	--	
Lacosamide	3	--	
Lamotrigine	3-15	--	
Levetiracetam	2	--	
Oxcarbazepine	2	10-hydroxycarbazepine	
Perampanel	14-21	--	95
Phenobarbital	14-21	--	
Phenytoin	7-28	--	90
Pregabalin	1-2	--	
Primidone	1-4	Phenobarbital	
Rufinamide	2	--	
Tiagabine		--	95
Topiramate	4-5	--	
Valproic acid	1-3	toxic	90-95, Saturable
Vigabatrin		--	
Zonisamide	5-15	--	

Antiseizyure Drugs Target Serum Concentration Ranges

Drug	Target Concentration Range
Phenobarbital	10 - 40 µg/mL
Clobazam	0.03 - 0.3 ng/mL
Clonazepam	20 - 70 ng/mL
Phenytoin	10 - 20 µg/mL
Ethosuximide	40 - 100 µg/mL
Carbamazepine	4 - 12 µg/mL
Gabapentin	2 - 20 µg/mL
Lamotrigine	4 - 20 µg/mL
Levetiracetam	12- 46 µg/mL
Tiagabine	0.02 - 0.2 µg/mL
Topimarate	5 - 20 µg/mL
Valproic acid	50 - 100 µg/mL
Vigabatrin	0.8 - 36 µg/mL
Zonisamide	10 - 40 µg/mL

Evaluation of Therapeutic Outcomes

1. **Clinical response is more important than the serum drug concentrations and involves:**

a. **Identifying the type and number of seizures.**

b. **Identifying adverse effects.**

2. **Patients should record the severity and the frequency of seizures.**

3. **Ascertain if the patient is truly seizure free.**

Evaluation of Therapeutic Outcomes

4. **Monitor patient long-term for co-morbid conditions, social adjustment (including Quality-Of-Life assessments), drug interactions, and adherence.**
5. **Screen periodically for co-morbid neuropsychiatric disorders (depression and anxiety).**

Personalized Pharmacotherapy

- **The most important aspect of ASD use is individualization of therapy.**
- **The following should be considered together:**

1. **Seizure type.**
2. **Concomitant medical problems (hepatic function, renal function, psychiatric diseases, other neurologic problems, …).**
3. **Concurrent medications.**
4. **Patient specific characteristics (age, gender, child-bearing ability, and ethnicity).**

Therapeutic Considerations in the Elderly

- **The elderly are often on polytherapy which may contribute to:**

a. **Increased sensitivity to neuro-cognitive effects.**

b. **Increased possibility of drug-drug interactions with ASDs that affect the cytochrome P450 (CYP450) system (carbamazepine, phenytoin, and valproic acid, …).**

Therapeutic Considerations in the Elderly

- **Hypoalbuminemia is common in the elderly which may cause problems with highly bound ASD (phenytoin, valproic acid, …).**
- **The elderly experience body mass changes, such as an increase in fat to lean body mass or decrease in body water, which can affect the drug volume of distribution and elimination half-life.**

Therapeutic Considerations in the Elderly

- **The elderly may have compromised renal or hepatic function that require ASD dosage adjustment.**
- **Lamotrigine is considered the medication of choice in elderly, because it has equal efficacy to carbamazepine and gabapentin, and is better tolerated than carbamazepine.**

Therapeutic Considerations in the Young

- **For neonates and infants, an increase in the total body water to fat ratio and a decrease in serum albumin and α-acid glycoprotein can result in volume of distribution changes that affect ASD elimination half-life.**
- **Children up to the age of 3 years have decreased renal elimination of ASDs, especially in neonates.**

Therapeutic Considerations in the Young

- **Hepatic activity is reduced in neonates and infants, but by age 2 to 3 years it becomes more than that of adults.**
- **Therefore, neonates and infants require lower doses of ASDs, while children require higher doses than adults.**
- **Therapeutic drug monitoring is especially important in the young (but the therapeutic blood levels range is not well-defined as in adults).**

Therapeutic Considerations in Women

- Some women develop "catamenial seizures" (just before and during the menstrual flow and at the time of ovulation), which may be due to a slight increase of estrogen relative to progesterone, or due to progesterone withdrawal.
- The risk is ~ 10% - 70% in women with epilepsy.
- Treatment: conventional ASDs are the primary agents.

Therapeutic Considerations in Women

- At menopause, seizures improve in frequency, particularly the catamenial seizures.
- Enzyme-inducing ASDs increase the metabolism of estrogen, progesterone, and testosterone.
- They also increase production of sex hormone-binding globulin, leading to decreases in the free fraction of these hormones.
- All of this lead to menstrual irregularity, infertility, sexual dysfunction, and polycystic ovary syndrome (PCOS).

Therapeutic Considerations in Women

- **Enzyme-inducing ASDs (carbamazepine and topiramate and oxcarbazepine at high doses, and possibly clobazam, felbamate, lamotrigine, and rufinamide) can cause treatment failures in women taking oral contraceptives due to increased metabolism of ethinyl estradiol and progestin.**
- **Valproic acid may affect sex hormone concentrations causing hyper-androgenism and polycystic changes.**

Therapeutic Considerations in Men

- Men with epilepsy have reduced fertility.
- Carbamazepine, oxcarbazepine, and valproic acid are associated with sperm abnormalities in men.
- Valproic acid may cause testicular atrophy resulting in reduced testosterone levels.
- Levetiracetam may slightly increase serum testosterone.
- Various ASDs may affect libido and sexual function in both men and women.

Clinical Considerations with Specific Drugs

Carbamazepine:

Mechanism of Action :

- **It enhances fast inactivation of voltage-gated Na^+ channels.**

Pharmacokinetics:

- **Fat may enhance absorption of carbamazepine.**
- **It is highly protein bound to α_1-acid glycoprotein and albumin.**

Clinical Considerations with Specific Drugs

- **The major metabolite of carbamazepine is carbamazepine-10,11-epoxide, has anticonvulsant activity (affected by use of enzyme-inducing or enzyme-inhibiting drugs).**
- **Carbamazepine induces its own metabolism (autoinduction). Its half-life starts decreasing 3 to 5 days after initiation of therapy, and induction is complete within 21 to 28 days.**

Clinical Considerations with Specific Drugs

Adverse Effects:

1. Neurosensory adverse effects (35%-50% of patients).
2. Nausea.
3. Hyponatremia: especially in the elderly - monitor serum sodium.
4. Persistent leukopenia (2%). Stop use if the WBC count drops to less than 2,500/mm^3 and the absolute neutrophil count drops to less than 1,000/mm^3.

Clinical Considerations with Specific Drugs

5. Teratogenic.
6. Chronic use decreases bone mineral density and 25-hydroxy (OH) vitamin D.
7. It may worsen absence seizures, and precipitate tonic-clonic seizures in patients with other generalized seizure types.

Clinical Considerations with Specific Drugs

Drug Interactions:

1. Carbamazepine induces the metabolism of primidone, phenytoin, ethosuximide, valproic acid, and clonazepam.
2. Propoxyphene, troleandomycin, and valproic acid may inhibit carbamazepine clearance and increase its steady-state levels.
3. Phenytoin and phenobarbital decrease SS concentration of carbamazepine by enzyme induction.

Clinical Considerations with Specific Drugs

4. **CYP3A4 inhibitors may potentially increase carbamazepine serum concentrations.**

Place in Therapy:

- **It is considered first-line in many seizure types: focal onset seizures, generalized tonic-clonic seizures, and mixed seizure types.**

Clinical Considerations with Specific Drugs

Phenytoin:

Mechanism of Action:

- **It inhibits voltage-gated Na^+ channels.**

Pharmacokinetics:

- **The oral absorption of phenytoin may be saturable at doses above 400 mg.**
- **IM fosphenytoin absorption is rapid and well tolerated.**

Clinical Considerations with Specific Drugs

- **Phenytoin is highly protein bound, and it is essential to know the patient's serum albumin level when interpreting serum phenytoin concentrations.**
- **Significant renal dysfunction will also alter phenytoin protein binding.**
- **It distributes to breast milk and it crosses the placenta.**

Clinical Considerations with Specific Drugs

- **Phenytoin is metabolized in the liver by CYP2C9 and CYP2C19.**
- **Phenytoin displays Michaelis–Menten pharmacokinetics, (or zero-order kinetics).**

  The metabolism of phenytoin saturates at doses used clinically, so that a small change in dose can result in a disproportionally large increase in serum concentrations, potentially leading to toxicity.

Clinical Considerations with Specific Drugs

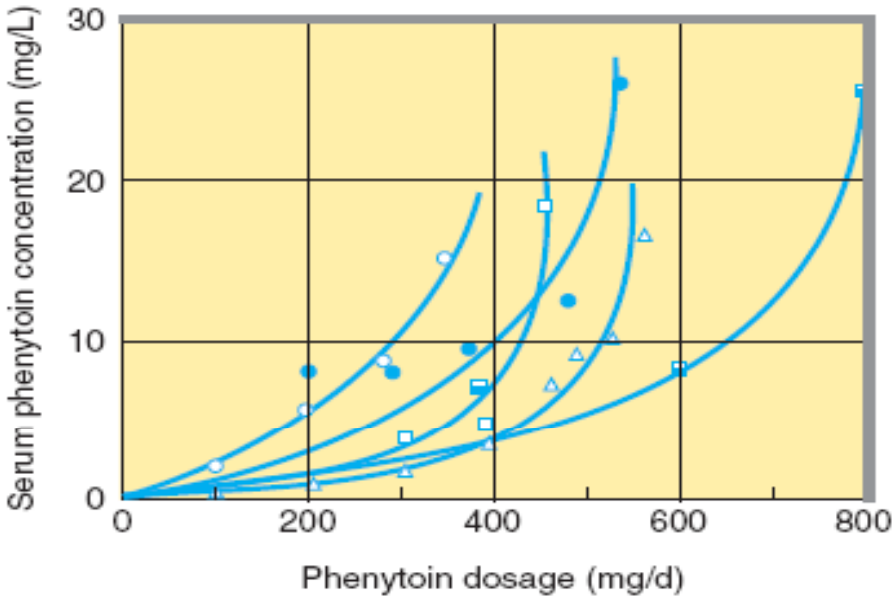


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]: *Quantitative Analytic Studies in Epilepsy.* Raven Press, 1977.)

Clinical Considerations with Specific Drugs

Adverse Effects:

1. CNS adverse effects are the most frequent.
2. At very high concentrations of greater than 50 µg/mL, it can exacerbate seizures.
3. Hypersensitivity and idiosyncratic reactions: rashes, Steven Johnson Syndrome, pseudolymphoma, bone marrow suppression, lupus-like reactions, and hepatitis.

Clinical Considerations with Specific Drugs

4. **With chronic use gingival hyperplasia (minimized by good oral hygiene), vitamin D deficiency, osteomalacia, carbohydrate intolerance, immunologic disturbances, hypothyroidism, and peripheral neuropathy.**

Clinical Considerations with Specific Drugs

Drug Interactions:

- **Phenytoin is an inducer of both CYP450 and UGT isozymes.**
- **It decreases folic acid absorption.**
- **Replacement of folic acid can reduce phenytoin concentration and result in loss of efficacy.**

Clinical Considerations with Specific Drugs

- **Phenylbutazone and sulfonamides can displace phenytoin from binding sites to plasma proteins.**
- **Hypoalbuminemia results in decreased total plasma drug concentration but not the free concentration.**
- **In these 2 cases intoxication may occur if total drug levels are increased by increasing the dose.**

Clinical Considerations with Specific Drugs

- **Phenobarbital and carbamazepine induce the metabolism of phenytoin.**
- **Isoniazid inhibits the metabolism of phenytoin.**

Place in Therapy:

- **Phenytoin is used for focal onset seizures and generalized tonic-clonic seizures.**

Clinical Considerations with Specific Drugs

Valproic Acid:

Mechanism of Action:

- **It may potentiate postsynaptic GABA responses.**

Pharmacokinetics:

- **Valproic acid is extensively bound to albumin, and binding is saturable at high concentrations, or in patients with hypoalbuminemia.**

Clinical Considerations with Specific Drugs

- **The primary pathway of valproic acid metabolism is β-oxidation, then glucuronidation.**
- **One of its metabolites (4-ene-VPA) may be increased with enzyme-inducing drugs, and may cause hepatotoxicity.**
- **It crosses into the placenta and attains high concentrations in fetal circulation.**

Clinical Considerations with Specific Drugs

Adverse Effects:

1. **GI adverse effects (nausea, vomiting, anorexia).**
2. **Alopecia.**
3. **Weight gain(20% of patients) may be associated with insulin resistance in obese patients.**
4. **Serious hepatotoxicity with deaths in patients younger than 2 years of age.**
5. **Thrombocytopenia.**
6. **Teratogenic.**

Clinical Considerations with Specific Drugs

Drug Interactions:

- Highly protein-bound drugs (free fatty acids, phenytoin, aspirin) can displace valproic acid.
- It displaces phenytoin from plasma proteins.
- It can inhibit specific CYP450 isozymes, epoxide hydrolase, and UGT isozymes.
- It inhibits the metabolism of phenobarbital, phenytoin, carbamazepine, and other drugs.

Clinical Considerations with Specific Drugs

- **It decreases clearance of phenobarbital (30%) and lamotrigine (50%) and can lead to their toxicity.**
- **Oral contraceptives may increase the clearance of valproic acid and lower serum levels by 20%.**
- **Meropenem can lower valproic acid levels.**

Clinical Considerations with Specific Drugs

Place in Therapy:

- **Valproic acid is first-line therapy for generalized seizures, including myoclonic, atonic, and absence seizures.**
- **It is also used in migraine headache and bipolar disorder.**

Clinical Considerations with Specific Drugs

Ethosuximide:

Mechanism of Action:

- **Inhibition of T-type Ca^{2+} channels.**

Adverse Effects:

- **Nausea and vomiting (40%), dose-related, which may be minimized by administration of smaller and more frequent doses.**

Disadvantages

- **It has a very narrow spectrum of activity.**

Clinical Considerations with Specific Drugs

Drug Interactions:

- **Valproic acid may inhibit ethosuximide's metabolism, when the metabolism of ethosuximide is near saturation.**

Place in Therapy:

- **It is a first-line treatment for absence seizures.**

Clinical Considerations with Specific Drugs

Lamotrigine:

Mechanism of Action:

- **Lamotrigine inhibits voltage-gated Na^+ channels.**
- **It modulates high voltage-gated Ca^{2+} channels.**
- **It modulates hyperpolarization-activated cation channels.**
- **It attenuates release of glutamate and to a lesser extent, GABA and dopamine.**

Clinical Considerations with Specific Drugs

Pharmacokinetics:

- Its half-life is prolonged in renal failure, and is dialyzable.

Adverse Effects:

1. CNS related ADRs are the most common .
2. A generalized, erythematous, and morbilliform rash.

- Steven Johnson Syndrome.
- Some rashes can necessitate the withdrawal of lamotrigine.

Clinical Considerations with Specific Drugs

Risk factors include:

a) Concomitant use of valproic acid.

b) High initial doses or rapid dosage escalation.

Drug Interactions:

- Valproic acid inhibits Its metabolism.
- Carbamazepine increased CNS adverse effects.
- Oral contraceptives reduce Its serum concentrations because of induction of glucuronidation by ethinyl estradiol.

Clinical Considerations with Specific Drugs

Place in Therapy:

- **Monotherapy and adjunctive treatment in patients with focal onset seizures, as a first- or second-line therapy.**
- **It is used in primary generalized tonic-clonic seizures and for primary generalized seizures of Lennox-Gastaut Syndrome (LGS).**

Clinical Considerations with Specific Drugs

Topiramate

Mechanism of Action:

- **It has multiple modes of action involving voltage-dependent Na^+ channels, $GABA_A$-receptor subunits, high-voltage Ca^{2+} channels, and kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subunits.**
- **It also inhibits carbonic anhydrase, which may have some antiseizure effects.**

Clinical Considerations with Specific Drugs

Pharmacokinetics:

- Dose should be adjusted in renal impairment.
- Metabolism is increased 50% when given with enzyme-inducing ASDs.

Adverse Effects:

- CNS effects are frequent (word-finding difficulties, problems with cognition).
- Kidney stones (1.5% of patients).
- Metabolic acidosis at doses as low as 50 mg/day.

Clinical Considerations with Specific Drugs

Drug Interactions:

- It increases phenytoin serum concentrations due to inhibition of CYP2C19.
- It may increase the clearance of valproic acid and the formation of its toxic metabolites.
- It increases the clearance of ethinyl estradiol at doses higher than 200 mg/day.

Clinical Considerations with Specific Drugs

Place in Therapy:

- **It is used as monotherapy or adjunctive therapy for focal onset seizures is patients 2 years or older.**
- **It is also used for tonic–clonic seizures in primary generalized epilepsy and generalized seizures in patients with LGS.**
- **It has benefit in patients with co-morbidities (migraines, obesity).**

Clinical Considerations with Specific Drugs

Gabapentin:

Mechanism of Action:

- **It elevates human brain GABA levels.**
- **It binds to the α2δ subunit of Ca^{2+} channels which may explain its analgesic effects.**

Pharmacokinetics:

- **It is eliminated by the kidney, and dosage adjustments is needed in renal impairment.**

Clinical Considerations with Specific Drugs

Adverse Effects:

- CNS effects, and weight gain.
- Aggressive behavior in children.
- A withdrawal reaction (anxiety, insomnia, nausea, sweating, and increased pain) in patients taking it for pain.

Drug Interactions:

- Cimetidine reduce clearance by 10%.
- Bioavailability is reduced by 20% by aluminum antacids.

Clinical Considerations with Specific Drugs

Place in Therapy:

- **It is used for focal onset seizures with or without secondary generalization in patients 3 years and older.**
- **It is useful in treating epilepsies with neuropathic pain.**

Clinical Considerations with Specific Drugs

Levetiracetam:

Mechanism of Action:

- **It binds to synaptic vesicle protein SV2A, in presynaptic terminals and inhibits neurotransmitter release.**

Pharmacokinetics:

- **Renal elimination mainly (66%).**
- **Dose should be reduced by 50% in severe liver cirrhosis.**

Clinical Considerations with Specific Drugs

- It is significantly excreted into breast milk.

Adverse Effects:

- CNS effects are the most common (agitation, irritability, or somnolence/lethargy).
- Behavioral problems can limit therapy in some patients.

Place in Therapy:

- Adjunctive therapy in focal onset seizures in patients 12 years of age or older, myoclonic seizures, and primarily generalized seizures.

Clinical Considerations with Specific Drugs

Zonisamide:

Mechanism of Action:

- It inhibits slow Na^+ channels and T-type Ca^{2+} channels , and possibly glutamate release.
- It has a weak carbonic anhydrase inhibitory effect.

Pharmacokinetics:

- It crosses the placenta, and the concentration in breast milk is similar to that in the plasma.

Clinical Considerations with Specific Drugs

Adverse Effects:

- Common CNS effects (sedation and effects on cognition).
- Paresthesias, modest weight loss, oligohidrosis and impaired body temperature control.
- Hypersensitivity reactions.
- Symptomatic renal stones.

Place in Therapy:

- It is used for the adjunctive treatment of focal onset seizures and may be considered first-line.