Preface

Drug interactions and adverse drug effects have received much attention since studies published in daily newspapers have shown that they result in upwards of 100,000 Americans each year being hospitalized or remaining hospitalized longer than necessary, as well as leading to the death of a number of patients. Use of multiple drugs (8–12 on average in hospitalized patients) is common in a number of therapeutic regimens. In addition to multiple drug therapy, a patient may have access to several prescribers, and may have predisposing illnesses or age as risk factors for interactions. Drug interactions may occur between prescription drugs, but also between food and drug, and chemical and drug. Whereas some may be adverse, interactions may also be sought to decrease side effects or to improve therapeutic efficacy.

Combining drugs may cause pharmacokinetic and/or pharmacodynamic interactions. Pharmacokinetic mechanisms of interaction include alterations of absorption, distribution, biotransformation, or elimination. Absorption can be altered when drugs that alter pH or motility are co-administered, as seen with certain antiulcer or antidiarrheal medications, or when drugs are chelators or adsorbents (tetracyclines and divalent cations, cholestyramine, and anionic drugs). Distribution variations can result from competition for protein binding (sulfa drugs and bilirubin binding to albumin) or displacement from tissue-binding sites (digitalis and calcium channel blockers or quinidine). Induction of gene expression (slow), activation or inhibition (much quicker) of liver and extrahepatic enzymes such as P450, and conjugating enzymes have long found a place of choice in the literature describing the potential for adverse drug interactions resulting from altered metabolism. For example, induction is well described with the major anticonvulsant medications phenytoin, carbamazepine, and barbiturates, whereas inhibition can occur with antimicrobials from the quinolone, the macrolide, and the azole families. Finally, excretion can also be modified by drugs that change urinary pH, as carbonic anhydrase inhibitors do, or change secretion and reabsorption pathways, as probenecid does. Pharmacokinetic interactions in general result in an altered concentration of active drug or metabolite in the body, modifying the expected therapeutic response.

A second form of interaction has received little attention because of its modeling complexity and perhaps the poor understanding of basic physiological, biochemical, and anatomical substrates for drug action. Pharmacodynamic interactions involve additive (1 + 1 = 2), potentiating (0 + 1 = 2), synergistic (1 + 1 = 3), or antagonistic (1 + 1 = 0)

effects at the level of receptors. Receptors are mainly proteins, such as enzymes (acetylcholinesterase, angiotensin-converting enzyme, for example), transport proteins (digitalis and Na^+/K^+ ATPase), structural proteins (colchicine and tubulin), or ion channels (Class I antiarrhythmics and voltage-dependent sodium channels). Large families of receptors to drugs involve signal transduction pathways and changes in intracellular second messenger concentrations (autonomic nervous system drugs and α, β, muscarinic receptors, for example). Finally, even less understood are interactions at the level of nucleic acids such as DNA and RNA, which can change the levels of expression of key proteins in target tissues (tolerance, tachyphylaxis of numerous central nervous system drugs).

Handbook of Drug Interactions: A Clinical and Forensic Guide addresses both types of drug interactions, emphasizing explanations when possible, and careful review of the general pharmacology. The result, we hope, will prove useful to health and forensic professionals as well as medical, pharmacy, nursing and graduate students alike.

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Chapter 2

Antiepileptic Drugs

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1. Introduction

1.1. Epidemiology of Epilepsy

Epilepsy is a chronic neurologic disorder characterized by recurrent seizures. Estimates indicate that approximately 120 in 100,000 people in the United States seek medical attention each year as the result of experiencing a seizure. Though not every patient that has a seizure has epilepsy, approximately 125,000 new cases of epilepsy are diagnosed every year *(1–3)*.

The incidence of epilepsy in the general population is highest in newborn and young children with a second peak occurring in patients older than 65 years. It has been suggested that there may be some genetic predisposition to the development of seizures and epilepsy. Although the incidence of epilepsy is higher among patients with mental retardation and cerebral palsy, neither condition is synonymous with epilepsy *(1)*.

1.2. Etiology

Epilepsy is recognized as a syndrome of disturbed electrical activity in the brain that can be caused by a variety of stimuli. This disturbed electrical activity leads to the development of seizures. Seizures occur because of the abnormal discharge of neurons within the central nervous system (CNS). Even slight abnormal discharges can destabilize the electrical homeostasis of neurons, thus increasing the propensity for other abnormal activity and the propagation of seizure activity *(3)*.

Precipitation of seizures in predisposed patients can occur as the result of a variety of inciting factors. Hyperventilation, sleep, sleep deprivation, and sensory and emotional stimuli have all been implicated. Hormonal changes associated with menses and several prescription drugs and drug classes may also influence the onset or frequency of seizure activity in patients with epilepsy. In addition, many antiepileptic drugs (AEDs) are known to cause seizures at excessive concentrations *(3)*.

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2. Medications Utilized in the Treatment of Epilepsy

AEDs act within the central nervous system in one of two ways: by reducing pathologic electrical discharges or by inhibiting the propagation of aberrant electrical activity. This may occur through effects on specific ion channels, inhibitory neurotransmitters, or excitatory neurotransmitters. Though multiple neurophysiological effects of AEDs have been theorized and hypothesized, it is important to recognize that the true mechanisms of action of these agents are poorly understood and may be multifactorial *(4)*.

Testing to determine the serum concentration of AEDs is commonly employed. The widespread availability of this technology makes the determination of serum concentrations an attractive method for use in forensic science. For most AEDs there is poor correlation between maintenance doses and their resulting serum concentrations *(5)*. In addition there is important interindividual variability in both therapeutic and toxic response to medications *(5–7)*. Therefore, knowledge of the pharmacokinetics of AEDs is essential for understanding and interpreting serum concentrations of AEDs. This includes issues related to all aspects of drug disposition: absorption, distribution, metabolism, and excretion.

This situation is further complicated by the fact that AEDs are subject to pharmacokinetic interactions with one another and many other drugs and foods *(5)*. Interactions with other drugs may lead to loss of efficacy or toxic effects from either the AED or the other interacting drug. This can be particularly important with the initiation or discontinuation of either drug and careful attention should be paid to the time course of initiation or discontinuation of any drug in the interpretation of the effects of drugs and serum drug concentrations *(8)*.

AEDs are well known for causing side effects. Side effects are generally classified as acute or chronic. Further, these effects may be described as being concentration dependent or idiosyncratic. Concentration-dependent effects are usually relatively common and well characterized. Allergic reactions are typically mild but may be severe in some cases. Other idiopathic reactions are rare but can be serious and life threatening *(9)*. Knowledge of the mechanism(s) of the toxic effects of AEDs and their relationship to serum concentration data are also important for the practicing forensic scientist.

Last, it is important to recognize that many AEDs are frequently employed for off-label use. The majority of off-label use involves the treatment of psychiatric disorders, particularly bipolar affective disorder or manic depressive disorder *(10)*. Other off-label uses include such things as migraine prophylaxis, attention-deficit disorder, and neuropathic pain.

2.1. Phenytoin and Fosphenytoin

2.1.1. Chemistry

Phenytoin is a hydantoin anticonvulsant medication that is structurally related to the barbiturates. Although similar, the monoacylurea structure of phenytoin makes it a much weaker organic acid than the barbiturates *(11)*. This results in very poor aqueous solubility of phenytoin.

Parenteral phenytoin must be formulated as a highly alkaline aqueous solution to maintain adequate solubility. This is accomplished through the use of an aqueous vehi-

cle consisting of 40% propylene glycol and 10% ethanol in water buffered with sodium hydroxide to a pH of 12. Parenteral phenytoin is incompatible with dextrose-based intravenous solutions. Preparation of intravenous phenytoin in dextrose-based solutions results in immediate precipitation of the free acid *(12)*.

Oral phenytoin is available in a variety of formulations as the free acid or sodium salt in both immediate- and extended-release formulations.

Fosphenytoin is a phenytoin prodrug. This drug was developed and formulated specifically to improve the solubility of phenytoin for parenteral use. Fosphenytoin is a disodium phosphate ester of phenytoin. As such, fosphenytoin is freely soluble in aqueous solution and is rapidly and completely converted to phenytoin in vivo through the action of serum phosphatase enzymes *(13)*.

2.1.2. Pharmacology

Phenytoin and fosphenytoin are effective at reducing seizure frequency and severity without causing generalized central nervous system depression. This action is mediated through effects on voltage-activated Na^+ channels in neuronal cell membranes *(11)*.

Depolarization of the neuronal cell membrane triggers the voltage-activated Na^+ channel to open, thus facilitating transmission of the action potential down the axon and, ultimately, from cell to cell. After opening, these voltage-activated Na^+ channels will spontaneously close. This is termed inactivation of the Na^+ channel. This inactivation is thought to cause the refractory period, a period of time after an action potential during which another action potential cannot be evoked *(11)*.

These drugs effectively limit repetitive firing of action potentials by prolonging inactivation, thus slowing the rate of repolarization of neuronal cells. At therapeutic concentrations, only neuronal cells that have been depolarized are protected from repetitive firing with no effect on spontaneous firing or responses to γ-aminobutyric acid (GABA) or glutamate *(14)*. This effectively limits the propagation of the aberrant electrical discharges that characterize epilepsy.

2.1.3. Pharmacokinetics

The pharmacokinetics of phenytoin (and also fosphenytoin) are strongly influenced by its limited aqueous solubility and saturable enzymatic elimination. The inactivation of these drugs by cytochrome P450 isozymes predisposes them to the influence of drug interactions.

2.1.3.1. Absorption

Because of its broad effectiveness in the management of epilepsy and the nature of epilepsy as a clinical disorder, phenytoin is available in a variety of formulations. Differences in physicochemical properties of the various formulations results in significant variability in both the rate and extent of absorption from each preparation.

Several factors including pK_a and lipid solubility, pH of the dissolution medium, solubility in the medium, and phenytoin concentration influence the rate and extent of absorption in the gastrointestinal tract. These factors are commonly altered by the presence of food or drugs in the gastrointestinal tract and the individual formulation *(12,13,15)*.

Phenytoin is poorly absorbed in the stomach due to the low pH of gastric juice (approximately 2.0), which renders it insoluble even though it may be present in a

nonionized form. The duodenum serves as the primary site of absorption with its higher pH increasing the solubility of the drug. Absorption slows within the jejunum and ileum and is again poor in the colon *(12,13,15)*.

Also because of poor solubility, intramuscular administration of phenytoin results in drug precipitation and the formation of an insoluble mass. This effect, coupled with the pain associated with intramuscular injection of a high-pH solution, mandate that phenytoin be administered intravenously when a parenteral route is necessary *(16)*.

Because of its improved solubility profile, fosphenytoin can be administered either intramuscularly or intravenously. Comparison of area under the curve measures for total or free phenytoin concentrations between fosphenytoin and phenytoin sodium are nearly identical, indicating complete bioavailability of fosphenytoin by either route *(13)*.

In an effort to facilitate simple and rapid utilization of parenteral fosphenytoin for the more problematic phenytoin, fosphenytoin is packaged and dosed as milligram phenytoin equivalents (mPEs) *(13)*. Although this facilitates accurate conversion between parenteral dosage forms, this conversion is less accurate when converting oral phenytoin to parenteral mPEs. This is because oral phenytoin is formulated as a sodium salt. Thus, a 100-mg capsule of phenytoin sodium delivers only 92 mg of actual phenytoin *(13)*. This represents an approximately 9% difference in total dose when oral phenytoin is converted to parenteral fosphenytoin or phenytoin. This may result in increased serum concentrations of phenytoin after conversion, particularly in light of the unpredictable nonlinear kinetics of phenytoin metabolism.

2.1.3.2. Distribution

Phenytoin is approximately 90% protein bound in the plasma, primarily to albumin. The remaining 10% is unbound or "free" phenytoin and is pharmacologically active because that which is bound to plasma proteins is unable to cross the blood–brain barrier. Because of the passive diffusion of phenytoin into the cerebrospinal fluid (CSF), the concentration of phenytoin in the CSF is considered equivalent to the unbound plasma concentration *(15)*.

The generally recognized therapeutic range for phenytoin is 10–20 µg/mL, which includes both bound and unbound drug. The 10% of phenytoin which remains unbound corresponds to an equivalent unbound therapeutic range of 1–2 µg/mL *(17)*.

Protein binding of phenytoin is dependent upon albumin concentration and can also be influenced by a variety of clinical conditions and situations. Low-serum albumin, renal failure, or concomitant use of other protein-bound drugs may change the protein binding and serum concentration of phenytoin *(17,18)*.

2.1.3.3. Metabolism

Phenytoin is extensively metabolized via the cytochrome P450 system. This occurs primarily through the 2C19 and 2C9 isozymes and accounts for the involvement of phenytoin in a variety of drug interactions *(12)*. Of note is the fact that the metabolism of phenytoin involves the intermediate formation of an arene oxide. This arene oxide intermediate has been implicated as the source of various toxicities and teratogenicity associated with the use of phenytoin *(19)*.

Phenytoin is also known for its nonlinear pharmacokinetics. At low doses, phenytoin exhibits a first-order dose-dependent kinetic profile. As the dose of phenytoin

increases, OH-phenytoin begins to inhibit CYP450D6, which is responsible for its own formation. This suicide inhibition leads to disproportionate and dramatic increases in serum concentration with relatively small changes in dosing rate *(12)*. In most patients, the usual therapeutic range exceeds the concentration at which metabolism is half-maximal, which causes phenytoin to exhibit a nonlinear profile in the majority of patients. A variety of situations such as concurrent illness, medications, pregnancy, age, or genetics may influence the maximal rate of metabolism and thus may alter the pharmacokinetic profile of phenytoin in a given patient *(20)*.

2.1.3.4. Excretion

Approximately 95% of an administered dose is excreted in the urine or feces as metabolites *(12,20)*.

2.1.4. Adverse Reactions

With initial therapy, the CNS depressant effects of phenytoin are most prominent and may cause lethargy, fatigue, incoordination, blurred vision, and drowsiness (Table 1). Slow-dose titration can minimize these effects *(9)*.

At high serum concentrations (greater than 20 μg/mL) many patients exhibit lateral gaze nystagmus. Other adverse effects known to occur at excessive plasma concentrations include ataxia, mental-status changes, and coma. Further, phenytoin has the ability to precipitate seizures or status epilepticus at extreme concentrations.

Chronic adverse effects include gingival hyperplasia, which can occur in up to 50% of patients receiving long-term therapy. Other long-term effects include hirsutism, acne, coarsening of facial features, vitamin D deficiency, osteomalacia, folic acid deficiency (with resultant macrocytosis), hypothyroidism, and peripheral neuropathy.

2.1.5. Contraindications and Precautions

Patients with hypersensitivity reactions to any hydantoin AED may react to other hydantoin AEDs such as phenytoin. In addition, some patients exhibit cross-sensitivity to other compounds with similar chemical structures such as barbiturates, succinimides, and oxazolidinediones.

Prenatal exposure to hydantoin AEDs may result in the development of cleft palate, cleft lip, cardiac malformations, and a constellation of physical abnormalities referred to as the fetal anticonvulsant syndrome: prenatal growth deficiency, microcephaly, hypophasia of the fingernails, and craniofacial abnormalities *(21)*.

The use of parenteral phenytoin can alter automaticity of cardiac tissue and may result in the development of ventricular arrhythmias and should only be used with extreme caution in patients with second- or third-degree arterio venous (AV) blockade, bradycardia, or significant cardiac disease *(22)*.

Because of the risk of myelosuppression, the use of phenytoin in immunosuppressed patients or patients with blood dyscrasias may increase the risk of infection or exacerbation of the hematologic abnormality.

The metabolism of phenytoin may be impaired in patients with active liver disease or active alcoholism with subsequent toxic effects associated with elevated serum concentrations *(6,12,23)*.

Table 1
Antiepileptic Drug Side Effects

	Acute Side Effects		
AED	Concentration Dependent	Idiosyncratic	Chronic Side Effects
Phenytoin	Ataxia	Blood dyscrasias	Behavior changes
	Nystagmus	Rash	Cerebellar syndrome
	Behavioral changes	Immunologic reactions	Connective tissue changes
	Dizziness		Skin thickening
	Headache		Folate deficiency
	Incoordination		Gingival hyperplasia
	Sedation		Hirsutism
	Lethargy		Coarsening of facial features
	Cognitive Impairment		Acne
	Fatigue		Cognitive impairment
	Visual Blurring		Metabolic bone disease
			Sedation
Carbamazepine	Diplopia	Blood dyscrasias	Hyponatremia
	Dizziness	Rash	
	Drowsiness		
	Nausea		
	Unsteadiness		
	Lethargy		
Lamotrigine	Diplopia	Rash	Not established
	Dizziness		
	Unsteadiness		
	Headache		
Valproic Acid	GI upset	Acute hepatic failure	Polycystic ovary-like
Sedation	Acute pancreatitis		syndrome
	Unsteadiness		Alopecia
	Tremor		Weight gain
	Thrombocytopenia		Hyperammonemia
Ethosuximide	Ataxia	Blood dyscrasias	Behavior changes
	Drowsiness	Rash	Headache
	GI distress		
	Unsteadiness		
	Hiccoughs		

(continued)

2.1.6. Drug Interactions

Phenytoin is involved in many drug interactions (Tables 2 and 3). These interactions are well characterized and phenytoin may be the target or cause of interactions. Pharmacokinetic drug interactions affecting absorption, metabolism, or excretion have the potential to either increase or decrease the plasma concentration of phenytoin. Though food may slightly alter the rate of absorption of phenytoin, it is well recognized that enteral feedings can dramatically decrease the bioavailability of phenytoin suspension when administered via a feeding tube *(24)*.

Although phenytoin is highly protein bound, protein-binding interactions are generally of minimal significance. As phenytoin is displaced from plasma proteins, the free

Table 1 (*continued*)

AED	Acute Side Effects: Concentration Dependent	Acute Side Effects: Idiosyncratic	Chronic Side Effects
Gabapentin	Dizziness Fatigue Somnolence Ataxia		Weight gain
Topiramate	Difficulties concentrating Psychomotor slowing Speech or language problems Somnolence, fatigue Dizziness Headache	Not established	Kidney stones
Felbamate	Anorexia Nausea Vomiting Insomnia Headache	Aplastic anemia Acute hepatic failure	Not established
Vigabatrin	Sedation Fatigue	Visual field defects Agitation Irritability Depression Psychosis	Not established
Levetiracetam	Sedation Behavioral Disturbance	Not established	Not established
Zonisamide	Sedation Dizziness Cognitive impairment Nausea	Rash Oligohydrosis	Kidney stones

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fraction of phenytoin increases. This is followed by an increase in the clearance of phenytoin, a decrease in total phenytoin concentration, and subsequent reestablishment of baseline free phenytoin concentration *(17)*. It is important that clinicians understand the mechanism of this interaction and do not react to decreases in total concentration without considering the possibility that free concentrations remain therapeutic.

Long-term use of phenytoin decreases folic acid absorption *(9)*. Replacement of folic acid effectively increases the clearance of phenytoin and thereby decreases phenytoin concentrations. Supplementation of folic acid, alone or as a vitamin, has the potential to decrease plasma phenytoin concentrations and subsequently decrease seizure control *(25)*.

2.2. Carbamazepine and Oxcarbazepine

2.2.1. Chemistry

The chemical structure of carbamazepine (CBZ) is tricyclic in nature, with two benzene rings flanking one azepine ring that contains a double bond. This structure is

Table 2
Interactions Between Antiepileptic Drugs*

AED	Added Drug	Effect[a,b]
Phenytoin (PHT)	Carbamazepine	Decr. PHT
	Felbamate	Incr. PHT
	Methosuximide	Incr. PHT
	Phenobarbital	Incr. or decr. PHT
	Valproic acid	Decr. Total PHT
	Vigabatrin	Decr. PHT
Carbamazepine (CBZ)	Felbamate	Incr. 10, 11 epoxide
	Felbamate	Decr. CBZ
	Phenobarbital	Decr. CBZ
	Phenytoin	Decr. CBZ
Oxcarbazepine	Carbamazepine	Decr. MHD
	Phenytoin	Decr. MHD
	Phenobarbital	Decr. MHD
Lamotrigine (LTG)	Carbamazepine	Decr. LTG
	Phenobarbital	Decr. LTG
	Phenytoin	Decr. LTG
	Primidone	Decr. LTG
	Valproic Acid	Incr. LTG
Valproic Acid (VPA)	Carbamazepine	Decr. VPA
	Lamotrigine	Decr. VPA
	Phenobarbital	Decr. VPA
	Primidone	Decr. VPA
	Phenytoin	Decr. VPA
Ethosuximide (ETX)	Carbamazepine	Decr. ETX
	Valproic acid	May incr. ETX
Gabapentin	No known interactions	
Topiramate (TPM)	Carbamazepine	Decr. TPM
	Phenytoin	Decr. TPM
	Valproic acid	Decr. TPM
Tiagabine (TGB)	Carbamazepine	Decr. TGB
	Phenytoin	Decr. TGB
Felbamate (FBM)	Carbamazepine	Decr. FBM
	Phenytoin	Decr. FBM
	Valproic acid	Incr. FBM
Vigabatrin	Phenytoin	Incr. PHT
Levetiracetam	No known interactions	
Zonisamide	Carbamazepine	Decr. zonisamide
	Phenytoin	Decr. zonisamide
	Phenobarbital	Decr. zonisamide

*From *(99)* with permission.
[a]Incr., increased; Decr., decreased.
[b]MHD, 10-hydroxy-oxcarbazepine.

Table 3
Interactions with Other Drugs*

AED	Altered by	Result[a]	Alters	Result[a]
Phenytoin (PHT)	Antacids	Decr. absorption of PHT	Oral contraceptives (OC)	Decr. efficacy of OC
	Cimetidine	Incr. PHT	Bishydroxycoumarin	Decr. anticoagulation
	Chloramphenicol	Incr. PHT	Folic acid	Decr. folic acid
	Disulfiram	Incr. PHT	Quinidine	Decr. quinidine
	Ethanol (acute)	Incr. PHT	Vitamin D	Decr. vitamin D
	Fluconazole	Incr. PHT		
	Isoniazid	Incr. PHT		
	Propoxyphene	Incr. PHT		
	Warfarin	Incr. PHT		
	Alcohol (chronic)	Decr. PHT		
Carbamazepine (CBZ)	Cimetidine	Incr. CBZ	Oral contraceptives (OC)	Decr. efficacy of OC
	Erythromycin	Incr. CBZ		
	Fluoxetine	Incr. CBZ	Doxycycline	Decr. doxycycline
	Isoniazid	Incr. CBZ	Theophylline	Decr. theophylline
	Propoxyphene	Incr. CBZ	Warfarin	Decr. warfarin
Oxcarbazepine			Oral contraceptives (OC)	Decr. efficacy of OC
Valproic Acid (VPA)	Cimetidine	Incr. VPA	Oral contraceptives (OC)	Decr. efficacy of OC
	Salicylates	Incr. free VPA		
Gabapentin	Cimetidine	Incr. gabapentin		
	Aluminum-containing antacids	Decr. gabapentin		
Topiramate (TPM)			Oral contraceptives (OC)	Decr. efficacy of OC
Tiagabine (TGB)	Cimetidine	Incr. TGB		
Felbamate (FBM)			Warfarin	Incr. warfarin

*From *(99)* with permission.
[a]Incr. increased; Decr. decreased.

most closely related to antipsychotic and antidepressant drugs such as chlorpromazine, imipramine, and maprotiline. CBZ differs from other heterocyclic AEDs by being tricyclic, lacking an amide group in the heterocyclic ring, and not possessing a saturated carbon atom in the cyclic structure *(26)*.

CBZ is insoluble in water although easily soluble in many organic solvents including benzene, chloroform, and dichloromethane. This lipophilicity strongly influences drug transport across biological membranes.

Oxcarbazepine, a biological prodrug, is a keto analog of CBZ. This change in structure alters the solubility of the compound and renders it only slightly soluble in chloroform, dichloromethane, acetone, and methanol whereas it is practically insoluble in water ethanol and ether *(27)*.

2.2.2. Pharmacology

CBZ enhances the inactivation voltage-activated Na^+ channels by slowing their recovery. This results in a net decrease in high-frequency repetitive firing of action potentials. These effects are evident and selective at serum concentrations within the therapeutic range *(28)*. No effect of carbamazepine on exogenously administered GABA or glutamate have been identified. The 10,11 epoxycarbamazepine metabolite also contributes a similar therapeutic effect *(29)*.

The pharmacologic effect of oxcarbazepine is due to a principal metabolite, 10-hydroxy-oxcarbazepine *(27)*. The mechanism of action is similar to that of carbamazepine but may also include increased potassium conduction and modulation of high-voltage calcium channels *(30,31)*.

2.2.3. Pharmacokinetics

It is well known that absorption of CBZ varies significantly from one dosage form to another *(32)*. Further, the effects of CBZ on the cytochrome P450 isozyme system warrants close assessment of the pharmacokinetics of this drug in clinical use.

2.2.3.1. Absorption

CBZ tablets are incompletely and erratically absorbed. The time to maximal serum concentration (t_{max}) is 8 or more h for tablets but 3–5 h for the suspension *(33)*. That means that the full effects of a given oral dose of carbamazepine tablets may not be recognized until 8 or more h after the dose has been ingested, whereas a similar dose of the suspension reaches maximal concentration in just 3–5 h and may influence the interpretation of serum concentration data. In addition to delayed absorption of carbamazepine from tablets, it has also been recognized that tablet formulations can be adversely affected by humidity and moisture content, thus further delaying or decreasing absorption *(34)*.

CBZ exhibits both zero-order and first-order absorption characteristics. Approximately 35% of an oral dose is absorbed in zero-order fashion (no effect of dose on absorption) whereas the remainder of the dose is absorbed according to a first-order kinetics. At doses greater than 20 mg/kg, an inverse relationship between dose and absorption begins to occur *(35)*.

Absolute bioavailability of CBZ is approximately 75% of the dose administered. This is similar between all dosage forms.

2.2.3.2. Distribution

CBZ is highly protein bound with 75 to 80% bound to albumin and other plasma proteins with an apparent volume of distribution of 0.8 to 2 L/kg. Unbound concentrations of CBZ vary inversely with the concentration of α_1-acid glycoprotein *(36)*.

CBZ is readily distributed into cerebrospinal fluid and these concentrations vary linearly with plasma levels. Although there may be wide variability in CBZ concentration between patients, the ratio of plasma:CSF concentration is relatively constant between patients *(37)*.

CBZ is also readily distributed into amniotic fluid and breast milk *(38)*. Although the use of CBZ is not contraindicated among pregnant women, it must be recognized that the newborn may be susceptible to adverse effects associated with exposure to CBZ.

Consistent with its lower lipid solubility, 10,11 epoxycarbamazepine has a lower apparent volume of distribution and increased fraction unbound of 48 to 53% *(39)*. The commonly accepted therapeutic range for CBZ in adults is 4 to 12 μg/mL *(40)*. To date, no accepted therapeutic range for the use of oxcarbazepine in treating epilepsy has been established *(41)*. Clinical trials in patients treated for neurologic pain have reported serum 10-hydroxy-carbazepine concentrations between 50 and 100 μg/mL *(42)*.

2.2.3.3. Metabolism

CBZ is essentially completely metabolized in humans through both oxidative and conjugative pathways. The primary metabolite, carbamazepine epoxide, is pharmacologically active and may accumulate in patients using CBZ over long periods of time *(36)*. This may potentially lead to the development of toxicity in a patient who manifests no change in plasma CBZ level after an increase in daily CBZ dose.

A comparison of patients reveals a lower ratio of CBZ epoxide to CBZ among patients receiving monotherapy when compared to those receiving multiple AEDs *(43)*.

2.2.3.3.1. Autoinduction. After initial dosing, CBZ induces its own metabolism significantly leading to increased clearance, decreased serum half-life, and a subsequent decline in plasma concentration over time. Studies have shown that whereas the elimination half-life of CBZ in single-dose studies varied from 20 to 65 h, the half-life was decreased by approximately 50% after multiple dosing for 10 to 20 d *(44,45)*.

There is a time dependence of CBZ kinetics secondary to this phenomenon of autoinduction. As the autoinduction progresses, changes in daily dose are required to maintain adequate plasma concentrations. Autoinduction is expected to be complete within 20 to 30 d and is dependent upon CBZ dose *(44,45)*.

2.2.3.4. Excretion

Approximately 72% of a given dose of CBZ is eliminated as metabolites in the urine. The remaining 28% is eliminated in the feces.

2.2.4. Adverse Reactions

The most common side effects of CBZ include dizziness, drowsiness, ataxia, dyskinesia, diplopia, and headache (Table 1). These effects are typically dose related and may resolve with continued administration only to recur with significant increases in plasma concentration *(9)*.

Idiopathic reactions to CBZ include blood dyscrasias and hypersensitivity reactions. Aplastic anemia, agranulocytosis, and pancytopenia have been reported to occur rarely with the use of CBZ and more often when CBZ is used in combination with other medications. Leukopenia is reported to occur in nearly 10% of patients. Though somewhat common, there appears to be no association between the presence of leukopenia and an increased incidence of infection. This has been hypothesized to occur as a result of white blood cell (WBC) redistribution *(9)*.

Hypersensitivity manifests most commonly as the development of an eczematous rash, which can progress in some patients to Stevens-Johnson syndrome *(46)*.

Dilutional hyponatremia and the syndrome of inappropriate antidiuretic hormone have been reported. The incidence of this phenomenon may increase with the age of the patient and appears somewhat dose related although low-dose therapy does not preclude the development of hyponatremia *(47)*.

2.2.5. Contraindications and Precautions

Some patients with a history of hypersensitivity to tricyclic antidepressants may be sensitive to CBZ and should only be treated with CBZ when the potential benefit outweighs the risk of hypersensitivity.

The use of CBZ in patients with absence seizures has been associated with worsening of seizures while using CBZ and should be avoided. Similarly, CBZ is considered ineffective for the treatment of Lennox-Gastaut syndrome *(11)*.

Congenital abnormalities have been reported to occur in infants of mothers who take CBZ. Current evidence indicates a higher risk of malformations with combination therapy, which may result in higher plasma CBZ concentrations *(48)*.

2.2.6. Drug Interactions

CBZs metabolic fate and its influence on the cytochrome p450 system make CBZ the subject of many significant drug interactions (Tables 2 and 3; *5*). Interestingly, valproic acid can effectively increase the plasma concentration of the 10,11-epoxide metabolite without changing the concentration of CBZ. Erythromycin inhibits the metabolism of CBZ resulting in clinically significant increases in plasma CBZ concentration. CBZ can induce the metabolism of many other drugs potentially leading to loss of therapeutic effect. Several examples include valproic acid, theophylline, warfarin, and ethosuximide.

2.3. Lamotrigine

2.3.1. Chemistry

Lamotrigine is a phenyltriazine AED unrelated to other currently available AEDs. As a tertiary amine, lamotrigine is only very slightly soluble in water, and slightly soluble in 0.1 *M* HCl *(49)*.

2.3.2. Pharmacology

Lamotrigine effectively inhibits the reactivation of voltage-activated Na^+ channels, similar to phenytoin and CBZ. Further, this action appears greater during repetitive activation, such as may occur during an epileptic seizure (double check that). However, unlike CBZ and phenytoin, lamotrigine also competitively blocks high-voltage

Ca^+ flux, by blocking presynaptic-type Ca^+ channels. Lamotrigine is also effective at inhibiting the release of glutamate and GABA from neurons, although this effect is much more pronounced for glutamate than for GABA *(49)*.

2.3.3. Pharmacokinetics

The pharmacokinetics of lamotrigine are unique when compared to other AEDs in that although it is not a subject of drug interactions related to oxidative metabolism through the cytochrome P-450 system, it is subject to interaction with drugs that may alter its glucuronide conjugation.

2.3.3.1. Absorption

Lamotrigine is readily and completely absorbed from the gastrointestinal system. The bioavailability is 98%. Plasma concentrations peak 1–3 h after oral administration and absorption appears to be linearly related to dose up to approximately 700 mg. Food does not alter the absorption of lamotrigine and systemic absorption can occur with rectal administration although to a more limited extent than with oral dosing *(50)*.

2.3.3.2. Distribution

Lamotrigine is approximately 56% bound to plasma proteins, which remains constant throughout the range of concentrations from 1 to 10 μg/mL. The apparent volume of distribution is 0.9–1.2 L/kg and is independent of dose administered. Although lamotrigine serum concentrations can be determined, no therapeutic range has been established for this drug and it is advised that treatment decisions be guided by therapeutic response without concern for serum concentration *(51)*.

2.3.3.3. Metabolism

Lamotrigine undergoes hepatic metabolism by uridine diphosphate (UDP)-glucuronosyl-transferase (UGT 1A4). Metabolism can occur at either heterocyclic nitrogen atom to form one of two glucuronide conjugates. These glucuronide conjugates are pharmacologically inactive *(51)*.

The half-life of lamotrigine is approximately 24–29 h in healthy volunteers. Though some evidence suggests that lamotrigine may undergo autoinduction, the relatively slow onset of autoinduction and the slow, tapered dosing schedule make this autoinduction clinically insignificant.

2.3.3.4. Excretion

Single-dose studies indicate that approximately 70% of a given dose is eliminated in the urine, almost entirely as glucuronide conjugates. Less than 10% of an administered dose is renally eliminated as unchanged drug *(51)*.

2.3.4. Adverse Reactions

Lamotrigine can cause a number of CNS side effects including drowsiness, ataxia, diplopia, and headache (Table 1). These effects occur significantly less frequently when compared to other AEDs *(52)*.

A hallmark side effect of lamotrigine is the development of a rash. Though several types of rash have been reported, the most common is a generalized erythematous morbilliform rash that is typically mild to moderate in severity. Case reports of the

development of Stevens-Johnson syndrome have been reported. Rash appears to occur more frequently in patients receiving concomitant valproic acid (VPA) and with rapid dose escalation *(53)*.

2.3.5. Contraindications and Precautions

Dermatologic reactions to lamotrigine appear to be more frequent in children when compared to adults. Safety and efficacy in patients up to the age of 16 years has not been proven. As noted previously the development of rash is more common among patients receiving valproic acid.

Significant interindividual differences in pharmacokinetics of lamotrigine have been observed in patients with renal dysfunction and careful consideration should be given that the benefits outweigh the risks of treatment in this patient population *(51)*.

2.3.6. Drug Interactions

Since lamotrigine is not metabolized by the cytochrome P450 system, it is not involved in precipitating cytochrome P450-based drug interactions. However, lamotrigine clearance is increased by phenytoin and CBZ. VPA decreases lamotrigine clearance and increases its half-life (Table 2). Conversely, the addition of lamotrigine to VPA can decrease VPA concentrations by as much as 25% *(51)*.

2.4. Valproate

2.4.1. Chemistry

Valproate is a short-chain branched fatty acid with low water solubility. Clinically, this compound is available as a sodium salt (valproate sodium Depakene®) with high water solubility and also as a complex of valproic acid and sodium valproate (divalproate Depakote®). This complex rapidly dissociates in the gastrointestinal tract to two molecules of valproate.

2.4.2. Pharmacology

Similar to phenytoin and carbamazepine, VPA prolongs the recovery of voltage-activated Na^+ channels. This effectively reduces propagation of rapid-firing action potentials. Some evidence exists to suggest that VPA blocks calcium currents in T-type calcium channels similar to that seen with ethosuximide *(54)*.

VPA has no direct modulatory effect on GABAergic neurotransmission. However, VPA may alter CNS GABA concentrations via two mechanisms. First, VPA may stimulate glutamic acid decarboxylase, thus increasing GABA synthesis. Second, valproic acid may inhibit the action of GABA transaminase and succinic semialdehyde dehydrogenase, therefore decreasing the degradation of GABA in the CNS. In either case, the net result is an increase in the concentration of GABA in the CNS *(54)*.

2.4.3. Pharmacokinetics

VPA is a widely used AED and is available in multiple formulations for oral and parenteral administration. Oral formulations include capsules, tablets, and syrup with immediate-release characteristics, enteric-coated tablets of sodium valproate or divalproex sodium, and enteric-coated sprinkles of divalproex sodium. Knowledge of the differences in pharmacokinetics between formulations is important.

2.4.3.1. Absorption

Oral VPA is essentially 100% bioavailable. However, because of difficulties associated with gastric irritation, enteric-coated and delayed-release formulations have been developed to improve tolerability *(54)*. Multiple oral formulations of VPA are available: immediate-release capsules, tablets, and syrup; enteric-coated tablets; and sprinkles of divalproex sodium. The rate of absorption of VPA differs among the various formulations *(54)*.

Immediate-release formulations are rapidly absorbed with peak concentrations reached within 2 h. Enteric-coated tablets delay absorption but remain rapid once the tablet reaches the small intestine. The time of onset for absorption of delayed-release formulations is dependent upon the state of gastric emptying with peak plasma concentrations occurring between 3 and 8 h after oral administration. In patients taking delayed-release VPA, true trough concentrations may not occur until after administration of a morning dose. No difference in bioavailabilty has been noted between immediate- or delayed-release formulations *(54)*.

2.4.3.2. Distribution

VPA is highly bound to plasma proteins with an apparent volume of distribution of 0.13–0.19 L/kg for adults and 0.2–0.3 L/kg in children. Protein binding is saturable at therapeutic concentrations and the free fraction of VPA increases with increasing total concentration. This effect can be quite dramatic with a threefold increase in total concentration leading to a near 10-fold increase in the concentration of free VPA *(5)*.

Serum concentrations of VPA are expected to be above 50 μg/mL to achieve therapeutic response. However, some controversy exists as to what the maximum concentration of the therapeutic range is. The most commonly cited maximal concentration of VPA is 100 μg/mL *(5)*. Though some reports have linked the emergence of adverse effects to concentrations greater than 80 μg/mL, higher concentrations may be required and tolerated in the management of difficult to control patients.

2.4.3.3. Metabolism

VPA is metabolized extensively by the liver with a glucuronide conjugate and a 3-oxo-VPA metabolite accounting for over 70% of an administered dose. One metabolite, a 4-ene-VPA causes marked hepatotoxicity in rats and may be responsible for reports of hepatotoxicity in humans although this has not been entirely substantiated. It should also be noted that higher concentrations of the 4-ene-VPA may be present in patients taking enzyme-inducing drugs such as phenobarbital *(54)*.

2.4.3.4. Excretion

The majority of VPA (70–80%) is excreted in the urine as metabolites. In addition, portions of VPA are excreted in bile (7%) and through the lung (2–18%) *(5)*.

2.4.4. Adverse Reactions

The most common side effects encountered with the use of VPA are mild and gastrointestinal in nature: nausea, vomiting, gastrointestinal distress, and anorexia (Table 1). CNS-related side effects such as drowsiness, ataxia, and tremor appear to be dose related. Any of these dose-related side effects may recur with changes in plasma concentration.

Hair loss is occasionally seen early in therapy but generally resolves with continued use *(5,9)*.

The most serious idiosyncratic effect of VPA is hepatotoxicity. Risk factors for death due to hepatotoxicity include age less than 2 years, mental retardation, and use of multiple AEDs. These events also occurred early in therapy *(55)*. Hyperammonemia is a very common finding among patients using VPA but is not considered to be a consequence of hepatic damage *(9,55)*. Pancreatitis is very rare.

Thrombocytopenia and other blood dyscrasias have been commonly reported to occur in patients receiving VPA but rarely lead to drug discontinuation. Bleeding can occur in some patients as a result *(56)*.

Excessive weight gain is a common side effect associated with chronic use of VPA *(9)*.

2.4.5. Contraindications and Precautions

Valproate crosses the placenta and observational studies have revealed that first-trimester use of valproate is associated with an increased risk of neural tube defects. Careful consideration of the use of this medication during pregnancy is warranted *(57)*.

Pediatric use of VPA is associated with an increased risk of hepatotoxicity. Risk factors include age less than 2 years, multiple-AED use, and mental retardation. In addition, VPA should not be used in patients with current hepatic disease *(9,55)*.

VPA does alter platelet aggregation *(9)*. Caution should be exercised when using VPA with other drugs that may affect platelet aggregation and by patients with a history of thrombocytopenia and other risk factors for bleeding.

The use of VPA in combination with lamotrigine significantly increases the risk of dermatologic reactions to lamotrigine and caution is warranted *(52)*.

2.4.6. Drug Interactions

Because VPA is extensively metabolized, alterations in liver enzyme function can change the clearance of VPA. Common enzyme-inducing drugs such as phenytoin, CBZ, primidone, and phenobarbital increase VPA metabolism (Table 2). Highly protein-bound drugs such as aspirin and phenytoin have a propensity to displace VPA from binding sites and may change plasma VPA concentrations (Table 3; *5*).

VPA inhibits the metabolism of phenobarbital resulting in a significant decrease in phenobarbital clearance and subsequent toxic effects. As mentioned previously, VPA has the potential to increase the concentration of the 10,11 epoxide metabolite of CBZ without altering the concentration of CBZ *(5)*.

2.5. Ethosuximide

Ethosuximide is indicated for the treatment of absence seizures. In this capacity, it is considered the drug of first choice. Combination therapy with VPA is indicated in patients with difficult to control absence seizures despite monotherapy with ethosuximide.

2.5.1. Chemistry

Ethosuximide is a monocyclic AED that contains a five-member ring structure with two carbonyl oxygen atoms flanking a ring nitrogen. This compound is considered

soluble in ethanol or ether, freely soluble in water or chloroform, and only very slightly soluble in hexane *(58)*. Though containing a chiral center, ethosuximide is utilized clinically as a racemic mixture of the two compounds.

2.5.2. Pharmacology

Ethosuximide exhibits antiseizure activity by reducing low-threshold Ca^{++} currents in the thalamic region. There is no effect on recovery of voltage-activated Na^{+} channels and thus no change in sustained repetitive firing. Ethosuximide has no influence on the action or concentration of GABA in the CNS. As a result of this unique mechanism of action, the use of ethosuximide is limited to the treatment of absence seizures *(59)*.

2.5.3. Pharmacokinetics

2.5.3.1. Absorption

Absorption of ethosuximide is rapid and nearly complete (90 to 95%) and does not appear to be effected by long-term administration. Peak concentrations are reached within 1 to 4 h after oral administration *(5,59)*. Although the rate of absorption of oral syrup may be faster than that of oral tablets, the formulations are considered bioequivalent.

2.5.3.2. Distribution

Ethosuximide distributes widely and homogeneously throughout the body. Based on this phenomenon, several studies have concluded that saliva concentrations of ethosuximide can be evaluated in lieu of plasma concentrations for therapeutic monitoring *(59,60)*.

The apparent volume of distribution is 0.62–0.65 L/kg in adults and 0.69 L/kg in children. Protein binding of ethosuximide is very low, ranging from 0 to 10% in humans *(60)*.

Serum concentrations of ethosuximide can be useful in monitoring therapy. The generally accepted therapeutic range is 40 to 100 μg/mL *(5,59)*.

2.5.3.3. Metabolism

Ethosuximide is extensively metabolized via hepatic oxidation with 80–90% of an administered dose transformed to inactive metabolites. Biotransformation is catalyzed through the action of CYP3A in a first-order fashion. Ethosuximide does not induce hepatic microsomal enzymes or the uridine diphosphate glucuronosyl transferase (UDPGT) system *(5,59)*.

2.5.3.4. Excretion

Approximately 10–20% of an administered dose of ethosuximide is renally eliminated with nonrenal routes accounting for the majority of elimination. The apparent half-life of the parent compound is 30–60 h in adults and 30–40 h in children *(58)*.

2.5.4. Adverse Reactions

Adverse reactions from use of ethosuximide are relatively benign when compared to other AEDs (Table 1). Most of these effects are dose related, predictable, and resolve with a decrease in dose. Nausea and vomiting occur in up to 40% of patients taking ethosuximide. CNS side effects such as drowsiness, dizziness, fatigue, lethargy, and hiccups

are also relatively common. Various behavioral changes have been reported but are not well correlated with ethosuximide use *(9,59)*.

Episodes of psychosis have been reported to occur in young adults with a history of mental disorders who are treated with ethosuximide. These psychotic reactions typically occur after the onset of seizure control and resolve after discontinuation of the drug and recurrence of seizures. This phenomenon is called forced normalization *(61)*.

Dermatologic adverse effects are the most common idiosyncratic reactions and range from mild dermatitis and rash to erythema multiforme and Stevens-Johnson syndrome *(62)*. Other rare effects include systemic lupus erythematosus, a lupus-like syndrome, and various blood dyscrasias *(63)*.

2.5.5. Contraindications and Precautions

Although teratogenic effects in humans have not been documented with the use of ethosuximide, caution is warranted as birth defects have been associated with the use of other AEDs.

Patients with active hepatic or renal disease may be at increased risk of side effects because of altered pharmacokinetics of ethosuximide.

2.5.6. Drug Interactions

Few drug interactions have been reported with ethosuximide. CBZ may induce the metabolism of ethosuximide resulting in loss of seizure control (Table 2). When ethosuximide metabolism reaches saturation, VPA may interfere by inhibiting the metabolism of ethosuximide and prolonging its half-life *(5)*.

2.6. Gabapentin

2.6.1. Chemistry

The chemical structure of gabapentin is that of GABA covalently bound to a cyclohexane ring. The inclusion of a lipophilic cyclohexane ring was employed to facilitate transfer of the GABA moiety into the central nervous system. Gabapentin is freely soluble in water *(64)*.

2.6.2. Pharmacology

Despite the fact that gabapentin was synthesized to serve as a GABA agonist in the CNS, this compound does not mimic the effects of GABA in experimental models *(65)*. Gabapentin appears to stimulate nonvesicular release of GABA through an unknown mechanism. Although it binds to a protein similar to the L-type voltage-sensitive Ca^{++} channels, gabapentin has no effect on calcium currents in root ganglion cells. Further, gabapentin does not effectively reduce sustained repetitive firing of action potentials as is seen with some other AEDs.

2.6.3. Pharmacokinetics

2.6.3.1. Absorption

Gabapentin is primarily absorbed in the small intestine. The L-amino acid carrier protein is responsible for absorption from the gut and distribution into the CNS. As a result of a saturable carrier-mediated absorption mechanism, bioavailability of gabapentin is dose-dependent *(66)*.

Oral bioavailability is reported as being 60%. In one multidose study of 1600 mg three times daily, bioavailability was reduced to approximately 35%. Maximal plasma concentrations are reached within 2 to 3 h of oral administration *(66)*.

2.6.3.2. Distribution

Gabapentin is not appreciably bound to plasma proteins and exhibits an apparent volume of distribution of 0.65–1.04 L/kg. CSF concentrations of gabapentin range from 10 to 20% of plasma concentrations and distribution is limited by active transport through the L-amino acid carrier protein *(66)*. Optimal concentrations for therapeutic response to gabapentin have not been established.

2.6.3.3. Metabolism

Gabapentin is not metabolized nor has it been found to interfere with the metabolism of other AEDs.

2.6.3.4. Excretion

Gabapentin is excreted exclusively in the urine. The reported half-life of gabapentin is 5–7 h but this may be significantly prolonged in patients with renal dysfunction *(67)*. Renal elimination of gabapentin is closely related to creatinine clearance and glomerular filtration rate. For this reason, dosage adjustments may be necessary for patients with renal disease.

2.6.4. Adverse Reactions

CNS side effects of gabapentin are the most common, tend to occur with initiation of therapy, and subside with continued use (Table 1). The most common of these effects are somnolence, dizziness, and fatigue. Ataxia has also been reported. Other rare CNS effects include nystagmus, tremor, and diplopia *(68)*.

Neuropsychiatric reactions including emotional lability, hostility, and thought disorders have been reported and may be more common among children and mentally retarded patients *(66)*. Weight gain is becoming more widely recognized as a long-term side effect of gabapentin use.

2.6.5. Contraindications and Precautions

Elderly patients or patients with impaired renal function should be monitored closely for the development of side effects secondary to reduced clearance and accumulation of gabapentin.

2.6.6. Drug Interactions

As previously mentioned, gabapentin is not appreciably metabolized by the cytochrome P450 system, nor does it alter the function of those enzymes. Cimetidine can decrease the renal clearance of gabapentin by 10% and aluminum-based antacids can decrease the bioavailability of gabapentin by as much as 20% (Table 3; *66*).

2.7. Topiramate

2.7.1. Chemistry

Topiramate is chemically unique from the more traditional AEDs in that it is a sulfamate-substituted monosaccharide. Topiramate is freely soluble in acetone, chloro-

form, dimethylsulfoxide, and ethanol. It is most soluble in aqueous environments with an alkaline pH *(69)*.

2.7.2. Pharmacology

Topiramate appears to have several mechanisms by which it exerts its antiseizure effects. First, topiramate reduces currents through voltage-gated Na^+ channels and may act on the inactivated state of these channels similarly to phenytoin, thus reducing the frequency of repetitive firing action potentials. In addition, topiramate increases postsynaptic GABA currents while also enhancing Cl^- channel activity. Further, topiramate decreases the activity of AMPA-kainate subtypes of glutamate receptors. Lastly, topiramate has been shown to function as a weak carbonic anhydrase inhibitor *(70,71)*.

2.7.3. Pharmacokinetics

2.7.3.1. Absorption

Topiramate is readily absorbed with an estimated bioavailability of 80%. Food may delay absorption but does not alter bioavailability. Time to peak concentration ranges from 1.5 to 4 h after an oral dose *(72)*.

2.7.3.2. Distribution

Topiramate is minimally bound to plasma proteins but does bind to erythrocytes. This unique phenomenon may lead to nonlinear changes in serum concentration until red cell binding sites have become saturated. The apparent volume of distribution is 0.6–0.8 L/kg *(72)*.

Topiramate dosage adjustments should be based upon therapeutic response as no defined therapeutic range has been established.

2.7.3.3. Metabolism

Topiramate metabolism accounts for the disposition of less than 50% of an administered dose. Hepatic metabolism involves several pathways including hydroxylation, hydrolysis, and glucuronidation. Administration of enzyme-inducing drugs such as CBZ can increase the apparent hepatic clearance of topiramate by 50–100% with a corresponding decrease in the fraction excreted in the urine *(73)*.

2.7.3.4. Excretion

Greater than 50% of an administered dose of topiramate is eliminated unchanged in the urine. The elimination half-life ranges from 15 to 24 h. Clearance of topiramate may be reduced in patients with renal failure *(70)*.

2.7.4. Adverse Reactions

Primary side effects of topiramate are usually related to either the CNS or carbonic anhydrase inhibition (Table 1). CNS side effects are common and patients may become tolerant to them with continued use. These include fatigue, somnolence, dizziness, ataxia, confusion, psychomotor retardation, and difficulty concentrating. Visual disturbances such as diplopia and blurred vision and acute closed-angle glaucoma have also been reported *(74)*.

Side effects related to carbonic anhydrase inhibition include paresthesias and nephrolithiasis. Paresthesias are generally mild and transient. Renal stones were reported to occur in 1.5% of patients in premarketing studies but have been less frequent in postmarketing analyses *(70)*.

Two unique side effects have been attributed to topiramate. In contrast to other AEDs, long-term use of topiramate is associated with a decrease in body weight from 1 to 6 kg. This weight loss typically begins within the first 3 mo of therapy and peaks between 12 and 18 mo of use. Higher degrees of weight loss tend to occur in patients with higher pretreatment weight *(70)*.

Lastly, some users of topiramate report difficulty with word finding while talking. This has been attributed to the effects on psychomotor function and is not a specific effect on language or speech *(74)*.

No significant metabolic, hematologic, or hepatic effects have been attributed to the use of topiramate.

2.7.5. Contraindications and Precautions

Topiramate has demonstrated various teratogenic effects in animal models. Postmarketing surveillance has identified select cases of hypospadias in infants born to women taking topiramate alone or in combination with other AEDs during pregnancy. Topiramate is classified in the FDA Pregnancy Category C *(69)*.

Patients with impaired renal function may be at risk of toxicity due to accumulation of topiramate and should be monitored appropriately.

2.7.6. Drug Interactions

Topiramate does not appear to alter the metabolism or elimination of other AEDs. CBZ induces the metabolism of topiramate thus necessitating adjustment of the dosage of topiramate when used concomitantly (Table 2). Other potent enzyme inducing drugs such as phenytoin or phenobarbital may exhibit similar effects. It should also be noted that dose adjustments would be necessary upon discontinuation of an enzyme-inducing drug while continuing the topiramate *(75)*.

2.8. Tiagabine

2.8.1. Chemistry

Tiagabine is a nipecotic acid derivative synthesized by linking nipecotic acid to a lipophilic anchor compound. The addition of this anchor compound facilitates transfer of the nipecotic acid moiety across the blood–brain barrier. Tiagabine is sparingly soluble in water and practically insoluble in most organic solvents. However, it does remain soluble in ethanol *(76)*.

2.8.2. Pharmacology

Tiagabine reduces GABA uptake into presynaptic neurons by inhibiting the GABA transport protein, GAT-1. Inhibiting the reuptake of GABA results in increased extracellular concentrations of GABA and a prolongation of the inhibitory effect of GABA on neurons *(77)*.

2.8.3. Pharmacokinetics

2.8.3.1. Absorption

Tiagabine is readily absorbed with oral bioavailability approaching 90%. Absorption is linear with maximum plasma concentrations occurring between 45 and 90 min after administration in the fasting state and after a mean of 2.6 h when taken with food. Though food may delay the absorption of tiagabine, the extent of absorption is unaffected. It is recommended by the manufacturer that tiagabine be administered with food to avoid side effects associated with high plasma concentrations *(78,79)*.

2.8.3.2. Distribution

Tiagabine is highly bound to plasma proteins (96%) and is widely distributed throughout the body. The apparent volume of distribution is 1 L/kg *(78,79)*.

Though no therapeutic range for tiagabine has been established, because of the risk of drug interactions the manufacturer suggests that monitoring concentrations of tiagabine before and after the addition or discontinuation of interacting drugs may be useful *(76)*.

2.8.3.3. Metabolism

Tiagabine is extensively metabolized in the liver via the CYP3A isozyme system with less than 2% of an administered dose excreted unchanged. The half-life of tiagabine ranges from 5 to 8 hours in patients receiving monotherapy but may be reduced to 2–3 h in patients taking enzyme-inducing medications *(80)*.

2.8.3.4. Excretion

Approximately 25% of an administered dose of tiagabine is eliminated in the urine with 40–65% of a dose eliminated in the feces within 3–5 d. This extended elimination may be due to enterohepatic recycling of tiagabine metabolites *(80)*.

2.8.4. Adverse Reactions

Side effects that occur more commonly with tiagabine than placebo include dizziness, asthenia, nervousness, tremor, diarrhea, and depression (Table 1). These side effects are usually mild and transient *(81)*.

More severe side effects such as ataxia, confusion, and itching or rash have been reported although rarely and should resolve upon discontinuation of tiagabine *(81)*.

2.8.5. Contraindications and Precautions

Animal teratogenicity studies demonstrate increased risks of embryo-fetal development abnormalities but no evidence of teratogenicity in humans has been seen. Tiagabine is classified as FDA Pregnancy Category C.

2.8.6. Drug Interactions

Many drugs are known to inhibit or induce the 3A isozyme family of the cytochrome system. The use of drugs that alter metabolism through these isozymes should be expected to alter the metabolism of tiagabine. Plasma concentrations of tiagabine will decrease with the addition of enzyme-inducing drugs such as CBZ and phenytoin

whereas concentrations will increase with the addition of enzyme-inhibiting drugs such as cimetidine (Tables 2 and 3; *77*).

Although tiagabine is highly protein bound, plasma concentrations are low enough that significant displacement interactions do not occur.

2.9. Felbamate

2.9.1. Chemistry

Felbamate is a dicarbamate AED with a chemical structure similar to that of meprobamate. Whereas meprobamate incorporates an aliphatic chain at the 2-carbon position, felbamate includes a phenyl group at that position. Felbamate is a lipophilic compound that is only very slightly soluble in water and increasingly soluble in ethanol, methanol, and dimethyl sulfoxide *(82)*.

2.9.2. Pharmacology

Felbamate has a dual mechanism of action, inhibiting excitatory neurotransmission and potentiating inhibitory effects. Felbamate inhibits NMDA-evoked responses in rat hippocampal neurons. In addition, felbamate potentiates the effects of GABA in the same cell line *(83)*. By decreasing the spread of seizures to other neurons and increasing the seizure threshold, felbamate exhibits broad effects on various seizure types.

2.9.3. Pharmacokinetics

2.9.3.1. Absorption

Felbamate is readily absorbed from the gastrointestinal tract. Neither the rate nor the extent of absorption is altered by the presence of food. Greater than 90% of an orally administered dose of felbamate or its metabolites can be recovered in the urine or feces *(82)*.

2.9.3.2. Distribution

Felbamate is approximately 20–25% bound to plasma proteins and this is independent of total concentration. It readily crosses the blood–brain barrier with CSF concentrations nearly equal to plasma concentrations in animal models. No significant displacement of other compounds from protein-binding sites occurs with the use of felbamate *(84)*. The apparent volume of distribution of felbamate is 0.7–1 L/kg.

Though no therapeutic range has been defined for felbamate, it is suggested that concentrations of phenytoin, CBZ, be monitored when used concurrently with felbamate *(85)*.

2.9.3.3. Metabolism

Approximately 50% of an administered dose of felbamate is metabolized in the liver by hydroxylation and conjugation. One metabolite, atropaldehyde, has been implicated in the development of aplastic anemia associated with the use of felbamate. Atropaldehyde has been shown to alkylate proteins, which produces antigens that can generate a dangerous immune response in some individuals. Variations in the metabolism of felbamate as well as detoxification of atropaldehyde make it very difficult to predict which patients may be subject to this dangerous effect *(82)*.

2.9.3.4. Excretion

Urinary excretion of unchanged felbamate accounts for the disposition of 30–50% of an administered dose. This fraction can decrease to 9–22% in patients with renal dysfunction. The apparent half-life of felbamate has been reported to be between 16 and 22 h. This half-life may increase in patients with decreasing renal function *(85)*.

2.9.4. Adverse Reactions

Gastrointestinal upset, headache, anorexia, and weight loss have been reported to occur commonly among patients using felbamate (Table 1). Though most adverse effects will subside over time, anorexia and insomnia are more likely to persist with continued use.

Less common side effects such as diplopia, dizziness, and ataxia have been reported. However, these side effects occur more commonly with polytherapy than monotherapy and may be related to the other medications used, particularly CBZ *(86)*.

Postmarketing surveillance identified an increased risk of the development of aplastic anemia and hepatic failure among users of felbamate. Emerging risk factors for the development of these reactions are history of cytopenia, AED allergy or significant toxicity, viral infection, and/or immunologic problems *(82)*.

2.9.5. Contraindications and Precautions

Cross-sensitivity between felbamate and other carbamate drugs has been demonstrated. Caution is advised when treating a patient with carbamate hypersensitivity with felbamate.

Two known animal carcinogens, ethyl carbamate (urethane) and methyl carbamate, are found in felbamate tablets as a consequence of the manufacturing process. Quantities of these substances have been shown to be inadequate to stimulate tumor development in rats and mice. The implications of this in humans remains unknown *(82,87)*.

Teratogenicity studies in rats and mice revealed decreased rat pup weight and increased mortality during lactation but no effects on fetal development were identified. Felbamate is classified as FDA Pregnancy Category C.

Patients suffering from blood dyscrasias characterized by abnormalities in blood counts, platelet count, or serum iron concentrations should not receive felbamate without close evaluation of the risks and benefits of its use. Similarly, patients with a history of or current bone marrow suppression should not receive felbamate. This would also apply to patients receiving chemotherapy with agents known to cause bone marrow suppression *(82,88)*.

Because of the synthesis of atropaldehyde during felbamate metabolism and subsequent potential for immunologic response, patients with hepatic disease may be at increased risk for exacerbation of their condition *(82)*.

Caution should be exercised when patients with a history of myelosuppression or hematologic toxicity to any medication are prescribed felbamate as these patients may be at increased risk of felbamate-induced hematologic toxicity.

2.9.6. Drug Interactions

Felbamate has been reported to inhibit the metabolism of both phenytoin and valproic acid (Table 2). As felbamate increases the metabolism of CBZ serum concentra-

tions decrease whereas epoxide metabolite concentrations increase. Doses of phenytoin, CBZ, and VPA should be decreased by approximately 30% when felbamate is coadministered *(86,89)*.

Enzyme inducers like phenytoin and CBZ can increase the metabolism of felbamate. Felbamate has also been shown to decrease the metabolism of phenobarbital and warfarin (Table 3; *86,89*).

2.10. Vigabatrin

2.10.1. Chemistry

Vigabatrin, γ-vinyl GABA, is a structural analog of GABA. Vigabatrin is a racemic mixture of *R*(−) and *S*(+) isomers in equal proportions with no evident optical rotational activity. Although this compound is highly soluble in water, it is only slightly soluble in ethanol or methanol and remains insoluble in hexane or toluene *(90)*.

2.10.2. Pharmacology

Vigabatrin has been shown to effectively increase CNS concentrations of GABA in both animal models and humans with epilepsy in a dose-dependent fashion. Increased concentrations of other markers of GABA concentration (homocarnosine) have also been reported to occur in patients taking vigabatrin. The proposed mechanism by which vigabatrin facilitates these increases is through the inhibition of GABA transaminase, the primary enzyme involved in GABA metabolism. This inhibition occurs in an irreversible manner *(90)*. Therefore, despite a relatively short half-life, vigabatrin can be administered on a once-daily basis.

2.10.3. Pharmacokinetics

2.10.3.1. Absorption

Vigabatrin is readily absorbed from the gastrointestinal tract. Peak concentrations occur within 2 h of oral administration. Oral bioavailability is reported to be approximately 60%. Food has no effect on either the rate or extent of absorption of vigabatrin *(91)*.

2.10.3.2. Distribution

Vigabatrin has an apparent volume of distribution of 0.8 L/kg. There is virtually no binding to plasma proteins. CSF concentrations of vigabatrin are approximately 10% of concentrations in plasma samples. Uniquely, vigabatrin distributes into red blood cells with subsequent red blood cell concentrations approximating 30 to 80% of plasma concentrations *(90,91)*.

2.10.3.3. Metabolism

No human metabolites of vigabatrin have been identified and no therapeutic range has been established *(90,91)*.

2.10.3.4. Excretion

The manufacturer reports that up to 82% of an orally administered dose is recovered unchanged in the urine. The terminal half-life of vigabatrin is approximately 7 h, which can be significantly prolonged in patients with renal dysfunction. Although it

has been suggested that doses of vigabatrin be reduced in patients with renal dysfunction, no guidelines in this regard have been published *(90,91)*.

2.10.4. Adverse Reactions

Vigabatrin is well tolerated with sedation and fatigue being the primary adverse effects associated with its use (Table 1). It has been shown to have no effect on cognitive abilities *(90,92)*.

Psychiatric and behavioral effects of vigabatrin have been reported. Agitation, irritability, depression, or psychosis have been reported in up to 5% of patients taking the drug with no prior history of psychosis *(90)*.

The development of visual-field defects has occurred in patients taking vigabatrin. These visual field defects are commonly asymptomatic and appear to be irreversible. The time course of the onset, relationship with dose, influence of other AEDs, and progression of visual-field deficits are unknown. It is suggested that patients treated with vigabatrin undergo visual-field testing regularly during therapy *(90)*.

2.10.5. Contraindications and Precautions

No evidence of carcinogenicity has been demonstrated in animal studies. Serious fetal neurotoxicity has been shown to occur in animal studies and vigabatrin is *not* recommended to be used during pregnancy *(90)*. Vigabatrin is classified as FDA Pregnancy Category D.

Vigabatrin should be used with caution in patients with aggressive tendencies or evidence of psychosis as these patients may be at higher risk for these types of episodes while using vigabatrin *(90,92)*.

Because the risk of accumulation, patients with impaired renal function or a creatinine clearance less than 60 mL/min should be monitored closely for the development of adverse effects *(92)*.

2.10.6. Drug Interactions

Few clinically significant drug interactions have been identified with vigabatrin. Vigabatrin use can increase serum concentrations of phenytoin by as much as 30% although the mechanism of this interaction is unknown (Table 2; *92*).

2.11. Levetiracetam

2.11.1. Chemistry

Levetiracetam is a unique AED that is chemically unrelated to any of the other currently available AEDs. This single *S*-enantiomer pyrrolidine compound is very soluble in water and decreasingly less soluble in chloroform or methanol, ethanol, and acetonitrile, and practically insoluble in n-hexane *(93)*.

2.11.2. Pharmacology

The mechanism of action of levetiracetam is distinct and unrelated to the effects of other AEDs. No evidence supports any effect on voltage-gated Na^+ channels or on GABA or benzodiazepine receptors. Levetiracetam has been shown to bind in a stereo-specific, saturable, and reversible manner to unknown binding sites in the CNS. These binding sites do appear to be confined to synaptic membranes in the CNS and not the

peripheral nervous system. Phenylenetetrazole and piracetam can effectively displace levetiracetam from these binding sites whereas there is no effect on binding caused by other antiepileptic drugs, picrotoxin, or bicuculline. Midazolam, a benzodiazepine receptor agonist, has no discernible effect on binding of levetiracetam to synaptic membranes *(94)*.

2.11.3. Pharmacokinetics

2.11.3.1. Absorption

Levetiracetam is readily and completely absorbed after oral administration. Peak concentrations occur within 20–120 min of administration. Clinical studies have shown that although food does not decrease the extent of absorption, it can cause a delay in time to peak concentration by up to 1.5 h and decrease the peak concentration by as much as 20% *(94)*.

2.11.3.2. Distribution

The apparent volume of distribution of levetiracetam is 0.7 L/kg. This drug and its metabolites are less than 10% bound to plasma proteins and protein displacement drug interactions are unlikely to occur. There has been no therapeutic range established for levetiracetam *(93,94)*.

2.11.3.3. Metabolism

Levetiracetam is minimally metabolized in humans via a hydrolysis reaction. This metabolism does not involve hepatic microsomal enzymes and therefore is unlikely to be involved in metabolic drug interactions *(95)*.

2.11.3.4. Excretion

Renal excretion of parent drug accounts for 66% of the disposition of an orally administered dose of levetiracetam with an additional 25% of administered dose eliminated renally as metabolites. The elimination half-life is 6–8 h and may be prolonged as much as 2.5 h in elderly subjects due to changes in renal function. In addition, half-life is prolonged in patients with documented renal disease *(95)*.

2.11.4. Adverse Reactions

Common adverse effects of levetiracetam include somnolence, dizziness, asthenia, and fatigue (Table 1). Somnolence has been reported in up to 45% of patients receiving the drug. Coordination difficulties including ataxia, abnormal gait, and incoordination are also more common with levetiracetam than placebo. Behavioral symptoms have also been reported and include reactions such as psychosis, agitation, anxiety, hostility, emotional lability, depression, and others. These adverse effects typically appear early in therapy and may resolve with dose reduction *(93)*.

Little information is available regarding idiosynchratic reactions on hematologic and hepatic systems.

2.11.5. Contraindications and Precautions

Animal studies show that levetiracetam can cause developmental abnormalities at doses near that used in humans (93). Levetiracetam is classified as FDA Pregnancy Category C.

Levetiracetam dose should be reduced in patients with evidence of renal function impairment.

2.11.6. Drug Interactions

Pharmacokinetic studies of levetiracetam indicate that no clinically significant interactions of this sort occur. Levetiracetam neither induces nor inhibits cytochrome P450 isozymes nor does it alter UDP-glucuronidation *(95)*.

2.12. Zonisamide

2.12.1. Chemistry

Zonisamide is a unique AED with a sulfonamide structure. This compound is only moderately soluble in water and 0.1 *N* HCl *(96)*.

2.12.2. Pharmacology

Zonisamide exhibits antiseizure effects similar to other AEDs. It has been shown to inhibit T-type calcium currents as well as prolonging the inactivation of voltage-gated Na^+ channels, thus inhibiting sustained repetitive firing of neurons. These mechanisms are similar to those of phenytoin and CBZ. In addition, zonisamide may have some minimal carbonic anhydrase inhibitory activity *(94,96)*.

2.12.3. Pharmacokinetics

2.12.3.1. Absorption

Peak serum concentrations occur within 2–6 h of administration of an oral dose of zonisamide. Food may prolong the time to peak concentration (4–6 h) but has no effect on the extent of absorption *(94,96)*.

2.12.3.2. Distribution

Studies indicate that zonisamide is 40 to 50% protein bound. In addition, zonisamide is extensively bound to erythrocytes with erythrocyte concentrations eight times higher than serum concentrations. This binding to erythrocytes is saturable and may result in disproportionate increases in serum concentration with a given change in dose at higher doses. The volume of distribution is reported to be 1.4 L/kg. No therapeutic range has been established *(94,97)*.

2.12.3.3. Metabolism

The primary route of metabolism of zonisamide is reduction to 2-sulfamoylacetyl phenol (SMAP) by the CYP3A4 isozyme system. A minor metabolic route involves hydroxylation and acetylation to 5-N-acetylzonisamide. Zonisamide does not induce its own metabolism *(94,97)*.

2.12.3.4. Excretion

Renal elimination is the primary route for clearance of zonisamide. Thirty-five percent of an administered dose is recovered unchanged whereas the remaining 65% is eliminated in the urine as metabolites. The terminal half-life of zonisamide is 63 h, which may be prolonged in patients with renal or hepatic dysfunction *(94,97)*.

2.12.4. Adverse Reactions

Adverse effects most common with the use of zonisamide include somnolence, dizziness, ataxia, anorexia, headache, nausea, and anger/irritability (Table 1). Other CNS effects include psychomotor slowing, difficulty concentrating, and word-finding difficulties *(94,98)*.

Severe reactions including Stevens-Johnson syndrome, toxic epidermal necrosis, hepatic failure, aplastic anemia, agranulocytosis, and other blood dyscrasias have been reported in patients taking sulfonamides and should be considered potential side effects of zonisamide *(94,98)*.

Oligohydrosis and hyperthermia have been reported to occur in 13 pediatric patients during the first 11 yr of marketing of zonisamide in Japan. Although zonisamide is not approved for pediatric use in the United States, it is important to recognize that oligohydrosis and hyperthermia are potential adverse effects associated with the use of zonisamide *(98)*.

2.12.5. Contraindications and Precautions

Studies in rats and mice have shown teratogenic effects when zonisamide is administered during organogenesis in pregnancy. Embryo lethality has been demonstrated during the treatment of cynomolgus monkeys. Strong caution is advised against the use of zonisamide during pregnancy. Zonisamide is categorized as FDA Pregnancy Category C *(96)*.

Oligohydrosis and hyperthermia were reported to occur in Japanese children treated with zonisamide but has not occurred in Caucasians.

Decreases in clearance will occur in patients with impaired renal function and zonisamide should only be used under close supervision in patients with a glomerular filtration rate of <50 mL/min. In addition, metabolism of zonisamide may be decreased in patients with hepatic dysfunction.

2.12.6. Drug Interactions

Although zonisamide is metabolized via the CYP3A4 isozyme system, it has not been shown to alter the pharmacokinetics of other drugs metabolized through that isozyme. In contrast, CBZ, phenytoin, fosphenytoin, and phenobarbital have been shown to increase the clearance of zonisamide (Table 2). The clinical impact of these interactions are unknown as no therapeutic level for zonisamide has been determined *(94,97)*.

2.13. Conclusion

Epilepsy is a common neurologic condition that affects patients of all ages, although the incidence is higher among the youngest and oldest segments of the population. Historically, antiepileptic drug use has been fraught with complications, some of which are attributable to the many pharmacokinetic drug interactions encountered with this group of medications. In addition to the pharmacokinetic interactions that occur with antiepileptic drugs, clinicians must remain well informed and aware of the possibility of pharmacodynamic interactions that can occur with other medications known to have similar pharmacologic and toxicologic actions.

The close of the 20th century brought several new drugs to market for the treatment of epilepsy. Though each of these new drugs brings promise to the generations of patients that suffer from epilepsy, none is without risk.

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